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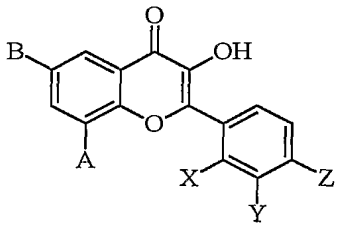
(54) Title: CDK INHIBITORS HAVING 3-HYDROXYCHROMEN-4-ONE STRUCTURE

(57) Abstract: The present invention relates to a novel 3-hydroxychromen-4-one derivative of formula (1), pharmaceutically acceptable salt, hydrate, solvate or isomer thereof which is useful as an inhibitor for Cyclin Dependent Kinase ("CDK"); to a process for preparing the compound of formula (1); and to a composition for suppression or treatment of cancer and diseases induced by cell proliferation such as inflammation, angiostenosis, angiogenesis, etc. comprising the compound of formula (1) as an active component together with pharmaceutically acceptable carriers.

CDK INHIBITORS HAVING 3-HYDROXYCHROMEN-4-ONE STRUCTURE

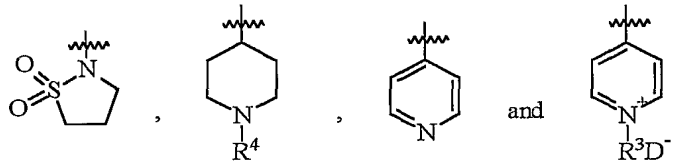
TECHNICAL FIELD

The present invention relates to a novel 3-hydroxychromen-4-one derivative represented by the following formula (1):



(1)

in which

A represents hydrogen or nitro, or represents amino which is optionally substituted by C_1-C_4-alkylcarbonyl or carbamoyl, or represents a structure selected from a group consisting of  wherein R^4 represents hydrogen or C_1-C_6-alkyl which is optionally substituted by amino or hydroxy, R^3 represents C_1-C_6-alkyl which is optionally substituted by amino or hydroxy, and D represents halogen,

B represents methyl, or represents amino which is optionally mono- or disubstituted by substituents selected from a group consisting of C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, acetyl, phenyl, benzyl and piperidinyl,

X, Y and Z independently of one another represent hydrogen, hydroxy, nitro,

cyano or halogen, or represent amino which is optionally substituted by C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl or carbamoyl, or represent C_1-C_4-alkyl which is optionally substituted by hydroxy or halogen,

pharmaceutically acceptable salt, hydrate, solvate or isomer thereof which is useful as an inhibitor for Cyclin Dependent Kinase (hereinafter, referred to as "CDK").

The present invention further relates to a process for preparing the compound of formula (1) and to a composition for suppression or treatment of cancer and diseases induced by cell proliferation such as inflammation, angiostenosis, angiogenesis, etc. which comprises the compound of formula (1) as an active component together with pharmaceutically acceptable carriers.

BACKGROUND ART

Researches on cell division process in molecular level have been extensively performed from the late 1980's through study of division of frog oocytes, analysis several yeast cell growth or characterization of induced mutants by radiation and study of the tumor suppressor Rb. In the 1990's, it was discovered that cell growth regulators of small size control the cell division process (i.e. growth, differentiation, cytogenesis, aging and apoptosis, etc.) through their own regulatory function. These results were very useful for more precise understanding of the pathology of several diseases. A representative example is cancer. In transformation process from normal cells to cancer cells, it was frequently observed that cell growth regulators lose their own function. That is, in cancer cells, the cell growth regulators show an abnormal activity, which is intimately associated with invasion/metastasis, the most crucial factor considered in the cancerpathology. Particularly, cell cycle deregulation is recognized to be a direct cause of cancer since cancer occurs when overexpression or knock-out of cell growth regulators is induced in the transformed

animals.

The cell growth is under positive or negative regulation in the same manner as other biological regulations. The major pathway of cell cycle regulation known up to now is based on CDK activity and as a result of studies on many cancer cells and carcinogenesis mechanisms, it was confirmed that problems of positive or negative regulation on CDK activity result in carcinogenesis in many cases. That is, cancer may occur when well-balanced regulation or timely regulation is upset.

The representative CDKs of mammals are CDK4(cyclin dependent kinase 4) which shows its activity in mid-G1 phase of cell cycle, CDK2 which shows its activity in mid-G1 and S phases, CDC2(CDK1) which shows its activity in G2-M phase. It has been known that CDK4 and CDK2 activities are regulated by check point of G1-S cell cycle and CDC2 activity by check point of G2-M. In many cancer cells, abnormalities appear in the regulatory mechanism of CDK4, CDK2 and CDC2(CDK1) and in fact, it was confirmed that artificially induced abnormalities cause cancer in the transformed animals. Therefore, the typical cyclin dependent kinases, i.e., CDK4, CDK2 and CDC2(CDK1) are suitable as a target of anti-cancer agents. Those kinases also become a target in developing an agent for suppression or treatment of cancer and diseases induced by cell proliferation such as inflammation, angiostenosis, angiogenesis, etc.

The results of studies on the relation between these CDKs and carcinogenesis will be explained in more detail in the following.

The relation between the abnormal regulation of CDK4 activity and carcinogenesis is observed in several cancer tissues. Deletion of p16 and p15 genes producing the proteins that inhibit CDK4 activity or overexpression of cyclin D1 that is essential for the CDK4 activity is observed in several kinds of cancer, which suggests that malignant phenotype may be induced when CDK4 activity is deregulated. Furthermore, it was

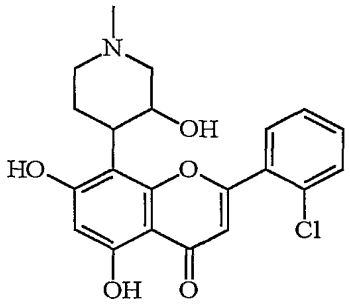
reported that p16 knocked-out mouse has such a high carcinogenesis rate as p53 knocked-out mouse, which suggests that malfunction of p16 on CDK4 regulation is a cause of carcinogenesis. From these experimental results, deregulation of CDK4 activity may be a certain cause of carcinogenesis and play a role in maintenance of phenotype of cancer cell. Therefore, it is highly probable that CDK4 inhibitors have an anti-cancer effect.

It was reported that overexpression of cyclin E that is essential for CDK2 activity is observed in some breast cancers, is deeply associated with metastasis of breast cancer, inhibits cell apoptosis under low serum condition, and induces anchorage independent growth, and that hyperproliferation and neoplasia of mammary epithelial cells are observed in transformed animal where CDK2 is overexpressed using MMTV promoter. This strongly suggests that CDK2 activity is related with the progress or maintenance of cell transformation and CDK2 inhibitors may have an anti-cancer effect.

Furthermore, it has been gradually discovered that CDC2(CDK1), CDK3, CDK5, CDK6, CDK7, etc. play an important role in each phase of cell division. These are classified into CDKs family. In addition to cyclin D1 and E, cyclin A, B, C, D2, D3, D4, F and G are also classified into the same family.

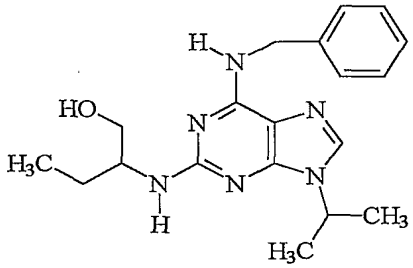
On the basis of the above-mentioned researches, efficient inhibitors against these CDKs are recognized to be useful as an anti-cancer agent. Therefore, recently, some inhibitors have been developed.

As the effective CDKs inhibitor developed hitherto, Flavopiridol (EP 0,241,003 (1987) and 0,366,061(1990)) represented by the following formula (2) can be mentioned:



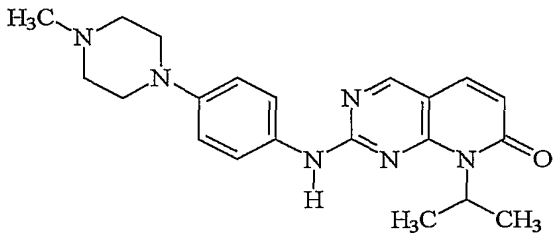
(2)

In addition, a purine derivative represented by the following formula (3):



(3)

has been reported(WO 97/20842), and a compound represented by the following formula (4):



(4)

having a quite different structure has been reported as an effective CDKs inhibitor(WO 98/33798).

DISCLOSURE OF INVENTION

However, the CDKs inhibitors developed up to now did not show satisfactory effects. Therefore, the present inventors have made extensive researches on CDKs inhibitors, particularly on flavone compounds and as a result, found that the above compound of formula (1) which has a quite different structure effectively inhibits the aforementioned CDKs and then, completed the present invention.

Therefore, the object of the present invention is to provide a novel 3-hydroxychromen-4-one derivative of formula (1), as defined above, pharmaceutically acceptable salt, hydrate, solvate or isomer thereof having an inhibitory activity for CDKs.

It is another object of the present invention to provide a process for preparing the compound of formula (1).

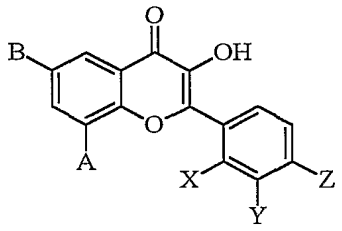
It is still another object of the present invention to provide a composition for suppression or treatment of cancer and diseases induced by cell proliferation such as inflammation, angiostenosis, angiogenesis, etc. comprising the compound of formula (1) as an active component together with pharmaceutically acceptable carriers.

In this specification, CDKs includes CDK2, CDK4, CDC2(CDK1), CDK3, CDK5, CDK6, CDK7, etc. and cyclins include cyclin D1, E, A, B, C, D2, D3, D4, F and G.

BEST MODE FOR CARRYING OUT THE INVENTION

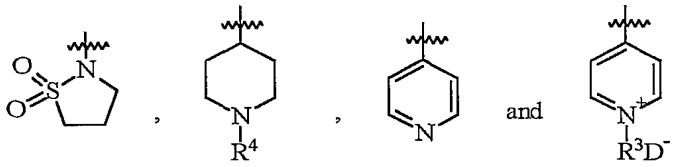
The present invention relates to a novel 3-hydroxychromen-4-one derivative

represented by the following formula (1):



(1)

in which

A represents hydrogen or nitro, or represents amino which is optionally substituted by C_1-C_4-alkylcarbonyl or carbamoyl, or represents a structure selected from a group consisting of  wherein R^4 represents hydrogen or C_1-C_6-alkyl which is optionally substituted by amino or hydroxy, R^3 represents C_1-C_6-alkyl which is optionally substituted by amino or hydroxy and D represents halogen,

B represents methyl, or represents amino which is optionally mono- or disubstituted by substituents selected from a group consisting of C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, acetyl, phenyl, benzyl and piperidinyl,

X, Y and Z independently of one another represent hydrogen, hydroxy, nitro, cyano or halogen, or represent amino which is optionally substituted by C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl or carbamoyl, or represent C_1-C_4-alkyl which is optionally substituted by hydroxy or halogen,

pharmaceutically acceptable salt, hydrate, solvate or isomer thereof which exhibits a suppressive and therapeutic effect for cancer and diseases induced by cell proliferation such as inflammation, angiostenosis, angiogenesis, etc. by the inhibition of CDKs activities.

Since the compound of formula (1) according to the present invention may have asymmetric carbon atoms depending on the substituents, they can be present in the form of individual enantiomers or diastereomers, or mixtures thereof including racemates. Thus, the present invention also includes all of these isomers and their mixtures.

Also, the compound of formula (1) according to the present invention can form a pharmaceutically acceptable salt. Such salt includes non-toxic acid addition salt containing pharmaceutically acceptable anion, for example a salt with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, hydriodic acid, etc., a salt with organic carboxylic acids such as tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid, trofluoroacetic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, maleic acid, etc., or a salt with sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, etc.

Typical examples of the compound of formula (1) according to the present invention are

8-amino-2-(3-amino-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one (Compound 1);

2-(4-hydroxy-3-nitrophenyl)-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one (Compound 2);

N-[2-(4-hydroxy-3-nitrophenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl] acetamide(Compound 3);

8-amino-2-(4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 4);

2-(3-amino-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 5);

N-[2-hydroxy-5-(3-hydroxy-6-methyl-4-oxo-4*H*-chromen-2-yl)phenyl]acetamide

(Compound 6);

N-{2-[4-hydroxy-3-(isopropylamino)phenyl]-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl}acetamide(Compound 7A);

N-[2-(3-amino-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]acetamide(Compound 7B);

2-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one (Compound 8);

8-amino-2-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one (Compound 9);

N-{5-[8-(ureido)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-2-yl]-2-hydroxyphenyl} urea(Compound 10);

8-amino-2-(4-aminophenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 11);

8-amino-3-hydroxy-2-(3-hydroxyphenyl)-6-methyl-4*H*-chromen-4-one(Compound 12);

3-hydroxy-6-methyl-2-(2,3,4-trihydroxyphenyl)-4*H*-chromen-4-one(Compound 13);

2-(2-bromo-3,4-dihydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one (Compound 14);

2-[3-hydroxy-2-(4-hydroxyphenyl)-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 15);

2-[2-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 16);

2-[2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 17);

2-[2-(3-bromo-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 18);

5-[8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-2-yl]-2-hydroxybenzonitrile(Compound 19);

2-[2-(2,4-dihydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 20);

2-[2-(3-chloro-4-fluorophenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 21);

2-[3-hydroxy-2-(4-hydroxy-3-methylphenyl)-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 22);

2-{3-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]-6-methyl-4-oxo-4*H*-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione(Compound 23);

2-[3-hydroxy-2-(4-hydroxy-3-trifluoromethylphenyl)-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 24);

2-[6-amino-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 25);

2-[6-(dimethylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 26);

2-[6-(diethylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 27);

2-[6-(benzylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 28);

2-[3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-6-(4-piperidinylamino)-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 29);

2-[6-(cyclohexylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 30);

2-[6-anilino-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 31);

2-[3-hydroxy-2-(4-hydroxyphenyl)-6-(methylamino)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 32);

2-{3-hydroxy-6-[(2-hydroxyethyl)(methyl)amino]-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione(Compound 33);

N-[2-(3-chloro-4-hydroxyphenyl)-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-3-

hydroxy-4-oxo-4H-chromen-6-yl]acetamide(Compound 34);

2-[6-amino-2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 35);

2-[2-(3-chloro-4-hydroxyphenyl)-6-(dimethylamino)-3-hydroxy-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 36);

2-[2-(3-chloro-4-hydroxyphenyl)-6-(methylamino)-3-hydroxy-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 37);

2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 38);

2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-8-(4-pyridinyl)-4*H*-chromen-4-one(Compound 39);

4-[2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1-methylpyridinium bromide(Compound 40);

2-(4-hydroxyphenyl)-3-hydroxy-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 41);

3-hydroxy-2-(4-hydroxy-3-methylphenyl)-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 42);

3-hydroxy-2-(4-hydroxy-3-trifluoromethylphenyl)-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 43);

2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-8-[1-(2-hydroxyethyl)-4-piperidinyl]-6-methyl-4*H*-chromen-4-one(Compound 44); and

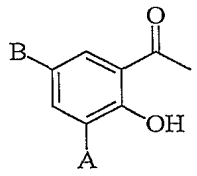
8-[1-(2-aminoethyl)-4-piperidinyl]-2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 45).

The compound of formula (1) of the present invention may be prepared by a process as described in the following and thus, it is another object of the present invention to provide such a process.

The compound of formula (1) of the present invention may be prepared

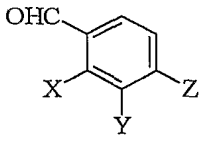
characterized in that

(a) a compound represented by the following formula (5):



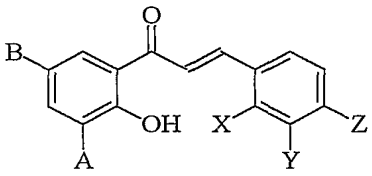
(5)

in which A and B are defined as previously described, is reacted with an aldehyde represented by the following formula (6):



(6)

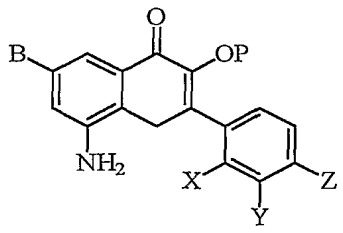
in which X, Y and Z are defined as previously described, to produce a compound represented by the following formula (7):



(7)

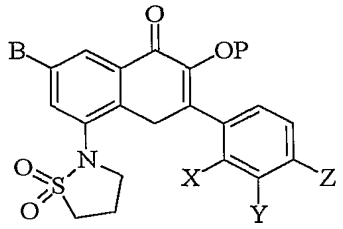
in which A, B, X, Y and Z are defined as previously described, and the compound of formula (7) thus prepared is cyclized in the presence of a base to produce the compound of formula (1);

(b) a compound represented by the following formula (8):



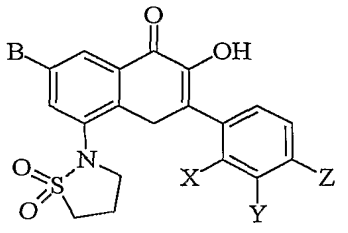
(8)

in which B, X, Y and Z are defined as previously described and P represents hydroxy-protecting group, preferably methyl or benzyl, is reacted with 3-chloropropanesulfonyl-chloride in the presence of a base and a catalyst to produce a compound represented by the following formula (9):



(9)

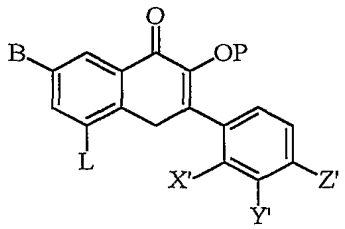
in which B, X, Y, Z and P are defined as previously described, and the compound of formula (9) thus prepared is deprotected to produce a compound represented by the following formula (1a):



(1a)

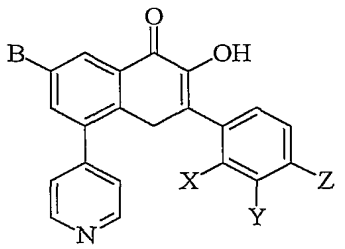
in which B, X, Y and Z are defined as previously described;

(c) a compound represented by the following formula (10):



(10)

in which B and P are defined as previously described, L represents leaving group, preferably halogen, and X', Y' and Z' each are identical with X, Y and Z, respectively, but hydroxy group(s) is(are) protected, is reacted with 4-halogenopyridine in the presence of a base and a catalyst and then deprotected to produce a compound represented by the following formula (1b):



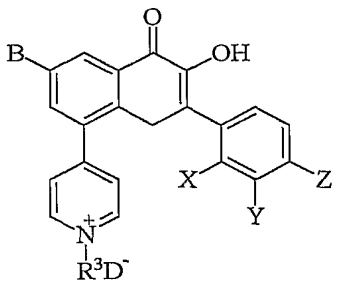
(1b)

in which B, X, Y and Z are defined as previously described;

(d) the compound obtained before the deprotection step in process variant (c) is reacted with a compound represented by the following formula (11):

R^3D (11) .

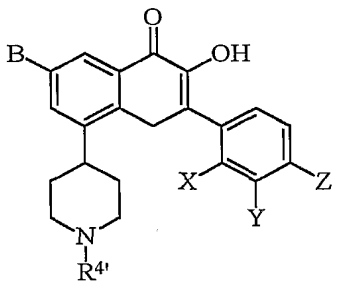
in which R^3 and D are defined as previously described, and then deprotected to produce a compound represented by the following formula (1c):



(1c) .

in which B, X, Y, Z, R^3 and D are defined as previously described;

(e) the compound obtained before the deprotection step in process variant (d) is reduced and deprotected to produce a compound represented by the following formula (1d):



(1d) .

in which B, X, Y and Z are defined as previously described and $R^{4'}$ is identical with R^4 but other than hydrogen;

or further hydrolysis, protection, deprotection, reduction or amidation reaction may be carried out.

Hereinafter, the process according to the present invention is more specifically

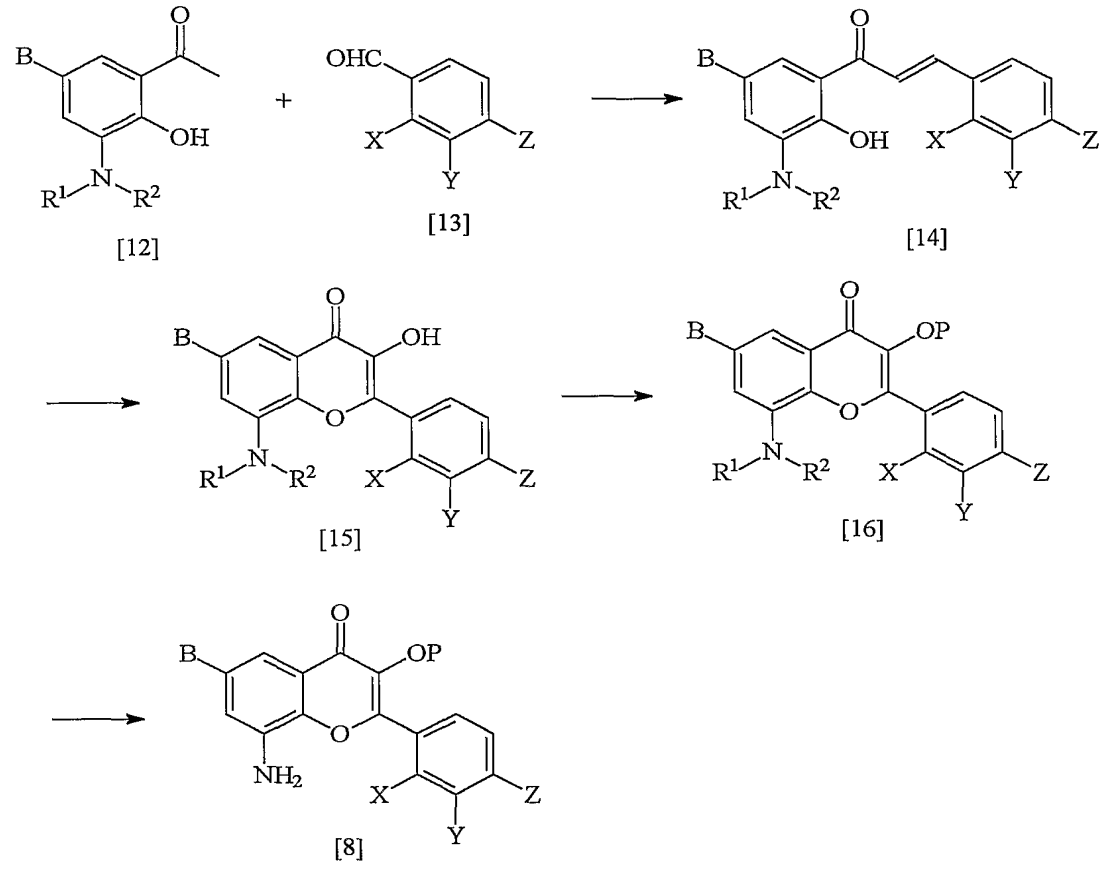
explained.

In process variant (a), the 2-hydroxyacetophenone derivative of formula (5) is reacted with 3 equivalents of the benzaldehyde derivative of formula (6) based on the compound of formula (5) to produce the compound of formula (7). As the base, 3 equivalents of sodium hydroxide based on the compound of formula (5) are preferably used. The reaction is preferably carried out in 80% aqueous ethanol solution for 3 hours at room temperature. Subsequently, the compound of formula (7) thus obtained is reacted in methanol solvent in the presence of excess 10% aqueous sodium hydroxide solution and excess hydrogen peroxide for 2 hours at room temperature to produce the compound of formula (1).

In process variant (b), the compound of formula (8) is dissolved in a solvent such as dichloromethane, reacted with 3-chloropropanesulfonylchloride in the presence of triethylamine and catalytic amount of dimethylaminopyridine at room temperature, and then concentrated. The resulting residue is dissolved again in dimethylformamide solvent and aqueous sodium hydroxide solution is added thereto. The mixture thus obtained is reacted for 30 minutes at 50℃ to produce the compound of formula (9). The compound of formula (9) is then reduced with hydrogen gas under a solvent system such as methanol/dichloromethane, or reacted with borontribromide in a solvent such as dichloromethane to produce the compound of formula (1a).

The compound of formula (8) used as a starting material in process variant (b) may be prepared according to the method as depicted in the following reaction scheme 1:

Reaction Scheme 1



in which

B, X, Y, Z and P are defined as previously described, and

R^1 and R^2 independently of one another represent hydrogen, oxo or acyl group, but both of them are not hydrogen.

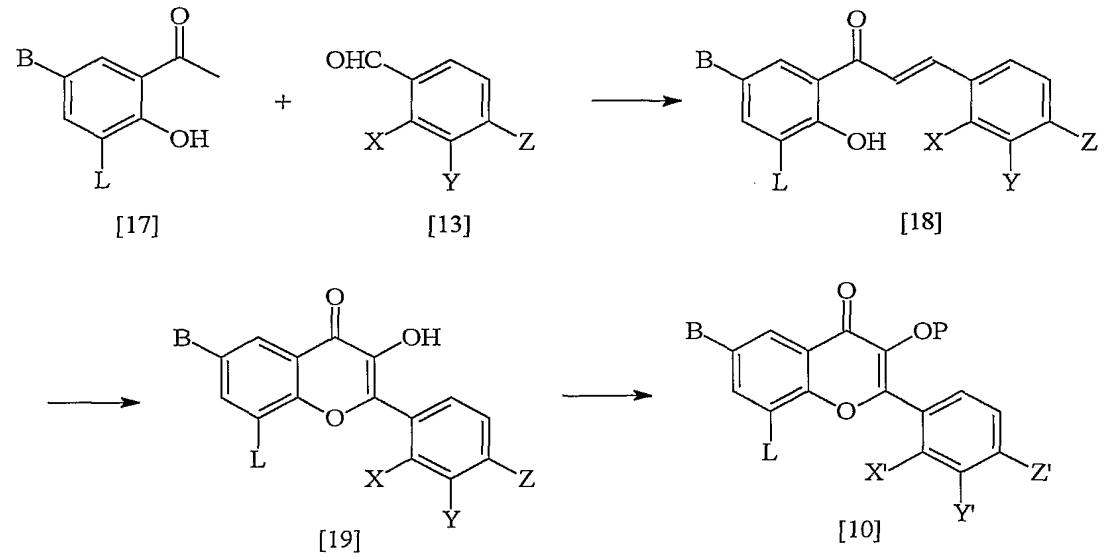
In the reaction scheme 1, the process for preparing the compound of formula (15) from the compound of formula (12) may be carried out according to the same procedure as process variant (a). The compound of formula (15) thus prepared is refluxed with iodomethane or benzyl bromide in acetone solvent in the presence of potassium carbonate to produce the compound of formula (16) wherein 3-hydroxy group on the chromene ring is protected by a group of methyl or benzyl. The compound of formula (16) wherein 8-

position of the chromene ring is substituted by nitro group is reduced by hydrogen gas. Otherwise, when the same position in the compound of formula (16) is substituted by acylamino group, BOC group is introduced into the amide group and the resulting compound is hydrolyzed to produce the compound of formula (8).

Process variants (c), (d) and (e) may be explained as follows. The starting compound of formula (10) is heated with 1.5 equivalent of bispinacolatodiboron, 3 equivalents of potassium acetate and 5mol% of dichlorobistriphenylphosphine palladium in N,N-dimethylformamide solvent under nitrogen atmosphere to 80 to 90℃ and reacted for 2 hours. The reactants are cooled to room temperature, reacted with 2 equivalents of 4-bromopyridine hydrochloride, 5mol% of dichlorobistriphenylphosphine palladium and 5 equivalents of 2M aqueous sodium carbonate solution for 15 hours, and then deprotected to produce the compound of formula (1b). The compound obtained before deprotection step to the formula (1b) is heated under reflux with 2 equivalents of the compound of formula (11) in acetone or acetonitrile solvent for 3 hours and then deprotected to produce the compound of formula (1c). Also, the compound obtained before deprotection step to the formula (1c) is dissolved in 50% methanol/dichloromethane, reacted with 5mol% of platinum oxide under room temperature and 1 atm of hydrogen atmosphere for 48 hours, and then deprotected to produce the compound of formula (1d). In process variants (c), (d) and (e), the deprotection step is carried out by adding the compound to dry dichloromethane, adding 5 equivalents of borontribromide thereto, and reacting for 10 hours at room temperature.

Further, the compound of formula (10) used as a starting material in process variants (c), (d) and (e) may be prepared according to the method as depicted in the following reaction scheme 2:

Reaction Scheme 2



in which

B, L, X, Y, Z, P, X', Y' and Z' are defined as previously described.

In reaction scheme 2, the compound of formula (17) is reacted with the benzaldehyde of formula (13) and 3 equivalents of sodium hydroxide in the solvent of 80% aqueous ethanol solution for 17 hours at room temperature to produce the compound of formula (18). This compound is reacted with 3 equivalents of 10% aqueous sodium hydroxide solution and 3 equivalents of hydrogen peroxide in methanol solvent for 3 hours at room temperature to produce the compound of formula (19). The compound of formula (19) thus obtained is reacted with 2 equivalents of iodomethane and potassium carbonate in acetone solvent for 30 minutes at room temperature to produce the compound of formula (10).

The reaction conditions including reaction solvent, base, amount of reactants, etc. in the process according to the present invention are not restricted to those as mentioned above and can easily be selected by optionally combining the various synthetic ways described in the present specification or known in the art. And such a combination may

be easily carried out by one of ordinary skill in the art. The following preparations and examples may also be referred to the specific reaction conditions of the above process.

After the reaction is completed, the product may be isolated and purified by conventional work up processes such as chromatography, recrystallization, etc.

The compound of formula (1) of the present invention can be effectively used as medicines for suppression or treatment of cancer and diseases induced by cell proliferation such as inflammation, angiostenosis, angiogenesis, etc. due to its excellent inhibitory activity against CDKs. Therefore, another object of the present invention is to provide a composition for suppression or treatment of cancer and diseases induced by cell proliferation such as inflammation, angiostenosis, angiogenesis, etc. characterized by comprising the compound of formula (1), pharmaceutically acceptable salt, hydrate, solvate or isomer thereof as an active component together with pharmaceutically acceptable carriers.

When the active compound according to the present invention is used for clinical purpose, it is preferably administered to the subject patient in an amount ranging from 1 to 50㎎ per ㎏ of body weight a day. The total daily dosage may be administered in one time or over several times. However, the specific administration dosage for the specific patient can be varied with the specific compound used, body weight of the subject patient, sex, hygienic condition, diet, time or method of administration, excretion rate, mixing ratio of the agent, severity of the disease to be treated, etc.

The compound of the present invention may be administered in the form of injections or oral preparations.

Injections, for example, sterilized aqueous or oily suspension for injection, can be prepared according to the known procedure using suitable dispersing agent, wetting agent,

or suspending agent. Solvents that can be used for preparing injections include water, Ringer's fluid and isotonic NaCl solution, and also sterilized fixing oil may be conveniently used as the solvent or suspending media. Any non-stimulative fixing oil including mono-, di-glyceride may be used for this purpose. Fatty acid such as oleic acid may also be used for injections.

As the solid preparation for oral administration, capsules, tablets, pills, powders and granules, etc., preferably capsules and tablets can be mentioned. It is also desirable for tablets and pills to be formulated into enteric-coated preparation. The solid preparations may be prepared by mixing the active compound of formula (1) according to the present invention with at least one carrier selected from a group consisting of inactive diluents such as sucrose, lactose, starch, etc., lubricants such as magnesium stearate, disintegrating agent and binding agent.

When the compound of the present invention is clinically administered for the purpose of treating cancer, the active compound of formula (1) may be simultaneously administered with one or more selected from the known anti-cancer agents. As the anti-cancer agent that can be administered together with the compound of the present invention, 5-fluorouracil, cisplatin, doxorubicin, taxol, Gemcitabine, etc. can be mentioned.

However, anti-cancer preparations containing the compound of the present invention are not limited to those as explained above, and any agent capable of preventing or treating cancer may be included.

The present invention will be more specifically explained in the following examples and experiments. However, it should be understand that these examples and experiments are intended to illustrate the present invention but not in any manner to limit the scope of the present invention.

Preparation 1

Synthesis of (*E*)-3-[4-(benzyloxy)-3-nitrophenyl]-1-(2-hydroxy-5-methyl-3-nitrophenyl)-2-propen-1-one

2-hydroxy-5-methyl-3-nitroacetophenone(200mg, 1.02mmol), 4-benzyloxy-3-nitrobenzaldehyde(300mg, 1.16mmol) and 3 equivalents of sodium hydroxide(120mg) were introduced into 80% aqueous ethanol solution and the resulting mixture was stirred for 3 hours at room temperature. The reaction solution was acidified by 2N hydrochloric acid solution and diluted with water. The resulting solid was filtered, washed with large amount of water and methanol, and then dried to give 430mg(Yield 97%) of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm); δ 8.06-7.75(5H, m), 7.60-7.15(7H, m), 5.31(2H, s), 2.43(3H, s)

FAB MS(m/e) = 435[M^++1]

Preparation 2

Synthesis of 2-[4-(benzyloxy)-3-nitrophenyl]-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 1(400mg, 0.92mmol) was introduced into methanol, and aqueous hydrogen peroxide(0.5㎖) and 10% aqueous sodium hydroxide solution(0.5㎖) were added thereto at room temperature. The resulting mixture was stirred for 2 hours at room temperature, acidified by 2N hydrochloric acid solution, and diluted with water. The solid having a pale yellow color thus obtained was filtered, washed with large amount of water and methanol, and then dried to give 200mg(Yield 48.5%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.84(2H, s), 8.44(1H, s), 8.19(2H, d), 7.34-7.17 (5H, m)

FAB MS(m/e) = 449[M^++1]

Example 1

Synthesis of 8-amino-2-(3-amino-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 1)

The compound prepared in Preparation 2(100mg, 0.22mmol) was dissolved in 10% methanol/dichloromethane solvent and catalytic amount of 10% Pd/C was added. The resulting mixture was reacted under hydrogen pressure of 50psi for 2 hours, filtered through a cellite pad, and concentrated to give 60mg(Yield 90%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.92(1H, s), 7.66(1H, s), 7.56(1H, d), 7.03 (1H, s), 6.81(2H, m), 5.51(2H, s), 2.32(3H, s)

FAB MS(m/e) = 299[M^++1]

Example 2

Synthesis of 2-(4-hydroxy-3-nitrophenyl)-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one(Compound 2)

The compound prepared in Preparation 2(20mg, 44.6μ mol) was dissolved in dichloromethane(2㎖), excessive amount of borontribromide was added, and the resulting mixture was reacted for 2 hours at room temperature. The remaining borontribromide was decomposed with methanol and then concentrated under reduced pressure. The solid thus obtained was washed with dichloromethane to give 15.6mg(Yield 98%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 10.86(1H, s), 9.26(1H, s), 8.60(1H, s), 8.35(2H, d), 7.36(1H, m), 7.10(1H, s)

FAB MS(m/e) = 359[M^++1]

Preparation 3

Synthesis of *N*-(3-{(*E*)-3-[4-(benzyloxy)-3-nitrophenyl]-2-propenoyl}-2-hydroxy-5-methylphenyl)acetamide

2-Hydroxy-5-methyl-3-acetamidoacetophenone(600mg, 2.89mmol) and 4-benzyloxy-3-nitrobenzaldehyde(890mg, 3.46mmol) were reacted according to the same procedure as Preparation 1 to give 590mg(Yield 46%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.48(1H, s), 8.19(1H, s), 7.84-7.70(3H, m), 7.60-7.00(9H, m), 5.31(2H, s), 2.41(3H, s), 2.23(3H, s)

FAB MS(m/e) = 447[M^++1]

Preparation 4

Synthesis of *N*-{2-[4-(benzyloxy)-3-nitrophenyl]-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl}acetamide

The compound prepared in Preparation 3(590mg, 1.32mmol) was reacted according to the same procedure as Preparation 2 to give 340mg(Yield 56%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 9.99(2H, br s), 8.77(1H, s), 8.53(1H, d), 7.77-7.40(7H, m), 5.44(2H, s), 2.42(3H, s), 2.19(3H, s)

FAB MS(m/e) = 461[M^++1]

Example 3

Synthesis of *N*-[2-(4-hydroxy-3-nitrophenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]acetamide(Compound 3)

The compound prepared in Preparation 4(15mg, 32μ mol) was reacted according to the same procedure as Example 2 to give 10mg(Yield 83%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 11.65(1H, br s), 9.97(1H, s), 9.86(1H, s), 8.78(1H, s), 8.42(1H, d), 7.74(2H, d), 7.32(1H, d), 2.42(3H, s), 2.19(3H, s)

FAB MS(m/e) = 371[M^++1]

Preparation 5

Synthesis of (*E*)-3-[4-(benzyloxy)phenyl]-1-(2-hydroxy-5-methyl-3-nitrophenyl)-2-propen-1-one

2-Hydroxy-5-methyl-3-nitroacetophenone(100mg, 0.51mmol) and 4-benzyloxybenzaldehyde(100mg, 0.47mol) were reacted according to the same procedure as Preparation 1 to give 150mg(Yield 75%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.19(1H, s), 7.84-7.70(4H, m), 7.60-7.00(9H, m), 5.31(2H, s), 2.41(3H, s)

FAB MS(m/e) = 390[M^++1]

Preparation 6

Synthesis of 2-[4-(benzyloxy)phenyl]-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 5(150mg, 0.38mmol) was reacted according to the same procedure as Preparation 2 to give 80mg(Yield 51%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.39(1H, s), 8.25(3H, m), 7.60-7.20(7H, m), 5.22(2H, s), 2.52(3H, s)

FAB MS(m/e) = 404[M^++1]

Example 4

Synthesis of 8-amino-2-(4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 4)

The compound prepared in Preparation 6(20mg, 49.6μ mol) was reacted according to the same procedure as Example 1 to give 11.9mg(Yield 85%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 10.03(1H, br s), 9.10(1H, br s), 8.21(2H, d), 7.03(1H, s), 6.92(2H, d), 6.83(1H, s), 5.58(2H, br s), 2.29(3H, s)

FAB MS(m/e) = 284[M^++1]

Preparation 7

Synthesis of (*E*)-3-[4-(benzyloxy)-3-nitrophenyl]-1-(2-hydroxy-5-methylphenyl)-2-propen-1-one

2-Hydroxy-5-methylacetophenone(200mg, 1.33mol) and 4-benzyloxy-3-nitrobenzaldehyde(350mg, 1.36mmol) were reacted according to the same procedure as Preparation 1 to give 170mg(Yield 29%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.19(1H, s), 7.84-7.70(4H, m), 7.60-7.00(9H, m), 5.31(2H, s), 2.41(3H, s)

FAB MS(m/e) = 390[M^++1]

Preparation 8

Synthesis of 2-[4-(benzyloxy)-3-nitrophenyl]-3-hydroxy-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 7(170mg, 0.43mmol) was reacted according to the same procedure as Preparation 2 to give 90mg(Yield 51%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 9.90(1H, br s), 8.75(1H, s), 8.48(1H, s), 7.90 (1H, s), 7.80-7.30(8H, m), 5.43(2H, s), 2.45(3H, s)

FAB MS(m/e) = 404[M^++1]

Example 5

Synthesis of 2-(3-amino-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 5)

The compound prepared in Preparation 8(25mg, 62μ mol) was reacted according to the same procedure as Example 1 to give 17mg(Yield 96%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 10.05(1H, s), 9.10(1H, s), 7.87(1H, s), 7.58 (4H, m), 7.50(1H, m), 7.30(1H, m), 6.83(1H, d), 2.44(3H, s)

FAB MS(m/e) = 284[M^++1]

Example 6

Synthesis of *N*-[2-hydroxy-5-(3-hydroxy-6-methyl-4-oxo-4*H*-chromen-2-yl)phenyl]acetamide(Compound 6)

The compound prepared in Example 5(10mg, 35μ mol) was dissolved in dichloromethane(2㎖) and reacted with excess acetic anhydride for 1 hour at room temperature. The mixture was concentrated and the residue was purified by silica gel column chromatography(eluent: 50% ethylacetate/hexane) to give 5mg(Yield 44%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 10.43(1H, s), 9.46(1H, s), 9.26(1H, s), 8.54 (1H, s), 7.88(2H, m), 7.59(2H, s), 7.03(1H, m), 2.44(3H, s), 2.23(3H, s)

FAB MS(m/e) = 326[M^++1]

Example 7

Synthesis of *N*-{2-[4-hydroxy-3-(isopropylamino)phenyl]-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl}acetamide(Compound 7A) and *N*-[2-(3-amino-4-hydroxy-phenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]acetamide(Compound 7B)

The compound prepared in Preparation 4(30mg, 65μ mol) was dissolved in 20% ethanol/dichloromethane(5㎖) and acetone(1㎖) and reacted under 10% Pd/C catalyst and hydrogen pressure of 50psi for 3 hours. The reaction solution was filtered through a cellite pad, concentrated, and purified by silica gel column chromatography(eluent: 70%

ethylacetate/hexane) to give 13mg(Yield 52%) of the title compound 7A and 7mg(Yield 31%) of the title compound 7B.

Compound 7A

^{1}H NMR($CDCl_3$, ppm); δ 8.09(1H, s), 7.62(1H, s), 7.40-7.20(5H, m), 6.76(1H, d), 2.36(3H, s), 2.18(3H, s), 1.93(1H, m), 1.17(6H, m)

FAB MS(m/e) = 383[M^++1]

Compound 7B

^{1}H NMR(DMSO-d_6, ppm); δ 9.78(1H, s), 9.10(1H, br s), 7.73(1H, s), 7.67(1H, s), 7.55(1H, s), 7.41(1H, d), 6.81(1H, d), 2.41(3H, s), 2.19(3H, s)

FAB MS(m/e) = 341[M^++1]

Preparation 9

Synthesis of (*E*)-3-(3-fluoro-4-methoxyphenyl)-1-(2-hydroxy-5-methyl-3-nitrophenyl)-2-propen-1-one

2-Hydroxy-5-methyl-3-nitroacetophenone(100mg, 0.51mmol) and 4-methoxy-3-fluorobenzaldehyde(95mg, 0.61mmol) were reacted according to the same procedure as Preparation 1 to give 127mg(Yield 74%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.54(1H, d), 8.40-8.20(3H, m), 7.28(3H, m), 3.89(3H, s), 2.48(3H, s)

FAB MS(m/e) = 332[M^++1]

Preparation 10

Synthesis of 2-(3-fluoro-4-methoxyphenyl)-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 9(127mg, 0.38mmol) was reacted according to the same procedure as Preparation 2 to give 80mg(Yield 60%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.54(1H, d), 8.40-8.20(3H, m), 7.28(1H, m), 3.89(3H, s), 2.48(3H, s)

FAB MS(m/e) = 346[M^++1]

Example 8

Synthesis of 2-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one(Compound 8)

The compound prepared in Preparation 10(80mg, 0.23mmol) was reacted according to the same procedure as Example 2 to give 44mg(Yield 57%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.39((1H, s), 8.26(1H, s), 8.03(1H, d), 7.97(1H, d), 7.13(1H, m), 2.41(3H, s)

FAB MS(m/e) = 332[M^++1]

Example 9

Synthesis of 8-amino-2-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 9)

The compound prepared in Example 8(11mg, 33μ mol) was reacted according to the same procedure as Example 1 to give 7.7mg(Yield 77%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.15(1H, d), 8.02(1H, d), 7.02(3H, m), 6.82 (1H, s), 5.62(2H, s), 2.29(3H, s)

FAB MS(m/e) = 302[M^++1]

Preparation 11

Synthesis of 3-(benzyloxy)-2-[4-(benzyloxy)-3-nitrophenyl]-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 2(100mg, 0.22mmol) was refluxed with 1.5 equivalent of benzylbromide and 2 equivalents of potassium carbonate in acetone for 10 hours. After the mixture was cooled to room temperature, it was filtered and concentrated. The residue was then dissolved in ethylacetate and washed with excess water and diethylether to give 100mg(Yield 84%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.62(1H, s), 8.45(1H, s), 8.30(1H, s), 8.27(1H, s), 7.69(1H, d), 7.50-7.28(10H, m), 5.44(2H, s), 5.18(2H, s), 2.54(3H, s)

FAB MS(m/e) = 539[M^++1]

Preparation 12

Synthesis of 8-amino-2-[3-amino-4-(benzyloxy)phenyl]-3-(benzyloxy)-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 11(100mg, 0.18mmol) was dissolved in acetonitrile(5㎖) and water(1㎖). Sodium hydrosulfite(370mg) and sodium bicarbonate (310mg) were added and the resulting mixture was stirred for 6 hours at room temperature. After concentration, the residue was washed with water(5㎖) and dichloromethane(1㎖) to give 35mg(Yield 40%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 7.46-7.25(13H, m), 6.90(1H, d), 6.83(1H, s), 5.16(2H, s), 5.08(2H, s), 2.37(3H, s)

FAB MS(m/e) = 479[M^++1]

Preparation 13

Synthesis of *N*-[5-[8-(ureido)-3-(benzyloxy)-6-methyl-4-oxo-4*H*-chromen-2-yl]-2-(benzyloxy)phenyl]urea

The compound prepared in Preparation 12(35mg, 73μ mol) was dissolved in dichloromethane(20㎖), triethylamine(0.1㎖) and triphosgene(80mg) were added at 0℃ and then stirred. After 1 hour, aqueous ammonia(0.3㎖) was added and the resulting

mixture was stirred for 30 minutes and then concentrated. The residue was dissolved in ethylacetate(15㎖), washed with water(15㎖), and then concentrated. The residue was washed with dichloromethane and 10% methanol/dichloromethane solution to give 25mg(Yield 60%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 9.20(1H, s), 8.76(1H, s), 8.15(2H, d), 8.05(1H, s), 7.75(1H, d), 7.48-7.18(11H, m), 6.92(1H, d), 6.50(2H, s), 6.32(2H, s), 5.31(2H, s), 5.16(2H, s), 2.39(3H, s)

FAB MS(m/e) =565 [M^++1]

Example 10

Synthesis of *N*-{5-[8-(ureido)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-2-yl]-2-hydroxyphenyl}urea(Compound 10)

The compound prepared in Preparation 13(25mg, 44.3μ mol) was reacted according to the same procedure as Example 2 to give 10mg(Yield 59%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 10.73(1H, s), 9.24(1H, s), 8.80(1H, s), 8.18(2H, d), 8.05(1H, s), 7.75(1H, d), 7.45(1H, s), 6.96(1H, d), 6.59(2H, s), 6.34(2H, s), 2.39(3H, s)

FAB MS(m/e) = 385[M^++1]

Preparation 14

Synthesis of (*E*)-1-(2-hydroxy-5-methyl-3-nitrophenyl)-3-(4-nitrophenyl)-2-propen-1-one

2-Hydroxy-3-nitro-5-methylacetophenone(100mg, 0.51mmol) and 4-nitrobenzaldehyde(116mg, 0.76mmol) were reacted according to the same procedure as Preparation 1 to give 155mg(Yield 92%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.36(1H, s), 8.32(2H, d), 8.19(2H, d), 8.10(2H, m), 7.93(1H, d), 2.40(3H, s)

FAB MS(m/e) = 329[M^++1]

Preparation 15

Synthesis of 3-hydroxy-6-methyl-8-nitro-2-(4-nitrophenyl)-4*H*-chromen-4-one

The compound prepared in Preparation 14(155mg, 0.47mmol) was reacted according to the same procedure as Preparation 2 to give 31mg(Yield 19%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 10.80(1H, br s), 8.50-8.20(6H, m), 2.52(3H, s)

FAB MS(m/e) = 343[M^++1]

Example 11

Synthesis of 8-amino-2-(4-aminophenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 11)

The compound prepared in Preparation 15(31mg, 90μ mol) was reacted according to the same procedure as Example 1 to give 7.3mg(Yield 27%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.06(2H, d), 7.61(1H, s), 7.02(1H, s), 6.81(1H, s), 6.66(2H, d), 5.51(2H, br s), 2.28(3H, s)

FAB MS(m/e) = 283[M^++1]

Preparation 16

Synthesis of (*E*)-3-[3-(benzyloxy)phenyl]-1-(2-hydroxy-5-methyl-3-nitrophenyl)-2-propen-1-one

2-Hydroxy-3-nitro-5-methylacetophenone(100mg, 0.51mmol) and 3-benzyloxybenzaldehyde(140mg, 0.66mmol) were reacted according to the same procedure as Preparation 1 to give 170mg(Yield 85%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.42(1H, s), 8.28(1H, s), 7.94(1H, s), 7.89(1H, d),

7.60-7.30(6H, m), 7.18(3H, m), 5.19(2H, s), 2.52(3H, s)

FAB MS(m/e) = 390[M^++1]

Preparation 17

Synthesis of 2-[3-(benzyloxy)phenyl]-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 16(170mg, 0.43mmol) was reacted according to the same procedure as Preparation 2 to give 90mg(Yield 51%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 10.20(1H, br s), 8.42(1H, s), 8.28(1H, s), 7.94(1H, s), 7.89(1H, d), 7.60-7.30(6H, m), 7.18(1H, d), 5.19(2H, s), 2.52(3H, s)

FAB MS(m/e) = 404[M^++1]

Example 12

Synthesis of 8-amino-3-hydroxy-2-(3-hydroxyphenyl)-6-methyl-4*H*-chromen-4-one(Compound 12)

The compound prepared in Preparation 17(20mg, 0.05mol) was reacted according to the same procedure as Example 1 to give 13mg(Yield 91%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 9.62(1H, s), 9.31(1H, br s), 7.74(2H, m), 7.33(1H, t), 7.06(1H, s), 6.87(2H, m), 5.54(2H, br s), 2.30(3H, s)

FAB MS(m/e) = 284[M^++1]

Preparation 18

Synthesis of (*E*)-3-[2-(benzyloxy)-3,4-dimethoxyphenyl]-1-(2-hydroxy-5-methylphenyl)-2-propen-1-one

2-Hydroxy-5-methylacetophenone(690mg, 2.53mmol) and 2-benzyloxy-3,4-

dimethoxybenzaldehyde(460mg, 3.03mmol) was reacted according to the same procedure as Preparation 1 to give 740mg(Yield 76%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 10.10(1H, s), 8.01(1H, s), 7.72(1H, d), 7.65-7.24(7H, m), 6.90(1H, d), 6.76(1H, d), 5.21(1H, s), 5.12(2H, s), 3.93(6H, s), 2.22(3H, s)

FAB MS(m/e) =405[M^++1]

Preparation 19

Synthesis of 2-[2-(benzyloxy)-3,4-dimethoxyphenyl]-3-hydroxy-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 18(740mg, 1.9mmol) was reacted according to the same procedure as Preparation 2 to give 370mg(Yield 47%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 7.90(1H, s), 7.55(1H, d), 7.44(1H, d), 7.27(1H, d), 7.25-7.14(5H, m), 5.07(2H, s), 3.89(3H, s), 3.82(3H, s), 2.43(3H, s)

FAB MS(m/e) =419[M^++1]

Example 13

Synthesis of 3-hydroxy-6-methyl-2-(2,3,4-trihydroxyphenyl)-4*H*-chromen-4-one(Compound 13)

The compound prepared in Preparation 19(13mg, 0.03mmol) was reacted according to the same procedure as Example 2 to give 5mg(Yield 53%) of the title compound.

^{1}H NMR(CD_3OD, ppm); δ 7.96(1H, s), 7.58(1H, d), 7.51(1H, d), 7.07(1H, d), 6.56(1H, d), 2.47(3H, s)

FAB MS(m/e) =301[M^++1]

Preparation 20

Synthesis of (*E*)-3-(2-bromo-3,4-dimethoxyphenyl)-1-(2-hydroxy-5-methylphenyl)-2-propen-1-one

2-Hydroxy-5-methylacetophenone(85mg, 0.57mmol) and 2-bromo-3,4-dimethoxybenzaldehyde(166mg, 0.68mmol) were reacted according to the same procedure as Preparation 1 to give 140mg(Yield 54.6%) of the title compound.

^{1}H NMR(CD_3OD, ppm); δ 7.93(1H, s), 7.58(1H, d), 7.52(1H, d), 7.35(1H, s), 7.18(1H, s), 6.77(1H, d), 6.52(1H, d), 3.91(3H, s), 3.79(3H, s), 2.46(3H, s)

FAB MS(m/e)=377[M^++1]

Preparation 21

Synthesis of 2-(2-bromo-3,4-dimethoxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 20(130mg, 0.34mmol) was reacted according to the same procedure as Preparation 2 to give 82mg(Yield 61.7%) of the title compound.

^{1}H NMR(CD_3OD, ppm); δ 7.94(1H, s), 7.60(1H, d), 7.53(1H, d), 7.38(1H, s), 7.23(1H, s), 3.91(3H, s), 3.79(3H, s), 2.46(3H, s)

FAB MS(m/e)=392[M^++1]

Example 14

Synthesis of 2-(2-bromo-3,4-dihydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 14)

The compound prepared in Preparation 21(30mg, 77μ mmol) was reacted according to the same procedure as Example 2 to give 18mg(Yield 64.4%) of the title compound.

^{1}H NMR(CD_3OD, ppm); δ 7.92(1H, s), 7.57(1H, d), 7.49(1H, d), 6.90-6.88 (2H,

m), 2.45(3H, s)

FAB MS(m/e)=363[M^++1]

Preparation 22

Synthesis of *N*-(3-{(*E*)-3-[4-(benzyloxy)-3-bromophenyl]-2-propenoyl}-2-hydroxy-5-methylphenyl)acetamide

2-Hydroxy-5-methyl-3-acetamidoacetophenone(1.7g, 8.2mmol), 4-benzyloxy-3-bromobenzaldehyde(2.6g, 8.9mmol) and 3 equivalents of sodium hydroxide(120mg) were introduced into 80% aqueous ethanol solution and stirred for 3 hours at room temperature. The reaction solution was acidified by 2N hydrochloric acid solution and diluted with water. The resulting solid was filtered, washed with large amount of water and methanol, and then dried to give 3.09g(Yield 78%) of the title compound as a yellow solid.

^{1}H NMR($CDCl_3$, ppm); δ 8.62(1H, s), 8.15-7.90(3H, m), 7.80-7.30(10H, m), 7.13(1H, d), 5.38(2H, s), 2.53(3H, s), 2.38(3H, s)

FAB MS(m/e) =480[M^++1]

Preparation 23

Synthesis of *N*-{2-[4-(benzyloxy)-3-bromophenyl]-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl}acetamide

The compound prepared in Preparation 22(3.09g, 6.45mmol) was introduced into methanol and then aqueous hydrogen peroxide(0.5㎖) and 10% aqueous sodium hydroxide solution(0.5㎖) were added at room temperature. The mixture was stirred for 2 hours at room temperature, acidified by 2N hydrochloric acid solution, and diluted with water. The resulting solid having a pale yellow color was filtered, washed with large amount of water and methanol, and then dried to give 2.96g(Yield 93%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 9.99(1H, br s), 9.80(1H, br s), 8.49(1H, s), 8.27(1H, s), 7.74(2H,m), 7.60-7.30(8H, m), 5.33(2H, s), 2.42(3H, s), 2.19(3H, s)

FAB MS(m/e) = 494[M^++1]

Preparation 24

Synthesis of *N*-{3-(benzyloxy)-2-[4-(benzyloxy)-3-bromophenyl]-6-methyl-4-oxo-4*H*-chromen-8-yl}acetamide

The compound prepared in Preparation 23(2.96g, 6mmol) was refluxed with 1.5 equivalent of benzylbromide and 2 equivalents of potassium carbonate in acetone for 10 hours. After the reaction mixture was cooled to room temperature, it was filtered and concentrated. The residue was dissolved in ethylacetate and washed with large amount of water and diethylether to give 1.96g(Yield 56%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.37(1H, s), 8.06(1H, s), 7.79(2H, m), 7.60-7.20(5H, m), 6.96(1H, d), 5.25(2H, s), 5.11(2H, s), 2.46(3H, s), 2.28(3H, s)

FAB MS(m/e) = 584[M^++1]

Preparation 25

Synthesis of 8-amino-3-(benzyloxy)-2-[4-(benzyloxy)-3-bromophenyl]-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 24(1.96g, 3.36mmol) was dissolved in dichloromethane(200㎖), di(t-butyl)dicarbonate(0.9g) and catalytic amount of dimethylaminopyridine were added, and the resulting mixture was stirred for 7 hours at room temperature. After completion of reaction, the solution was concentrated. The residue was dissolved in methanol(100㎖) and 2.5N aqueous sodium hydroxide solution(5 ㎖) was added thereto. The resulting mixture was stirred for 10 minutes at room temperature and concentrated. The residue was dissolved in ethylacetate, washed with water, and the extract was concentrated. The residue was dissolved in a solvent mixture of dichloromethane and trifluoroacetic acid(1:1, v/v), reacted for 2 hours at room temperature, and then concentrated under reduced pressure to give 1.6g(Yield 88%) of the

title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.35(1H, s), 8.11(1H, d), 7.51-7.28(11H, m), 7.06(1H, s), 6.87(1H, s), 5.34(2H, s), 5.07(2H, s), 2.31(3H, s)

FAB MS(m/e) = 542[M^++1]

Preparation 26

Synthesis of 2-{3-(benzyloxy)-2-[4-(benzyloxy)-3-bromophenyl]-6-methyl-4-oxo-4*H*-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 25(100mg, 0.18mmol) was dissolved in dichloromethane(5㎖), 2.5 equivalents of 3-chloropropanesulfonylchloride, 3 equivalents of triethylamine and catalytic amount of dimethylaminopyridine were added thereto, and the resulting mixture was reacted for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dimethylformamide(5㎖). 1N aqueous sodium hydroxide solution(2㎖) was added and the resulting mixture was reacted for 30 minutes at 50℃, acidified by 2N hydrochloric acid solution and diluted with water. The resulting solid was filtered and washed with large amount of water and diethylether to give 80mg(Yield 67%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.32(1H, s), 8.04(2H, d), 7.63-6.97(12H, m), 5.23(2H, s), 5.08(2H, s), 3.84(2H, t), 3.41(2H, t), 2.61(2H, m), 2.47(3H, s)

FAB MS(m/e) = 646[M^++1]

Example 15

Synthesis of 2-[3-hydroxy-2-(4-hydroxyphenyl)-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 15)

The compound prepared in Preparation 26(30mg, 46.5μ mol) was dissolved in 10% methanol/dichloromethane solvent, catalytic amount of 10% Pd/C was added, and the resulting mixture was reacted under hydrogen pressure of 50psi for 2 hours. The mixture

was filtered through a cellite pad and the filtrate was concentrated to give 14.8mg(Yield 82%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 10.10(1H, s), 9.40(1H, s), 8.13(2H, d), 7.87(1H, s), 7.68(1H, s), 6.94(2H, d), 3.87(2H, t), 3.49(2H, t), 2.55(2H, m), 2.45(3H, s)

FAB MS(m/e) = 388[M^++1]

Preparation 27

Synthesis of (*E*)-3-(3-fluoro-4-methoxyphenyl)-1-(2-hydroxy-5-methyl-3-nitrophenyl)-2-propen-1-one

2-Hydroxy-5-methyl-3-nitroacetophenone(100mg, 0.51mmol) and 4-methoxy-3-fluorobenzaldehyde(95mg, 0.61mmol) were reacted according to the same procedure as Preparation 22 to give 127mg(Yield 74%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.54(1H, d), 8.40-8.20(3H, m), 7.28(3H, m), 3.89(3H, s), 2.48(3H, s)

FAB MS(m/e) = 332[M^++1]

Preparation 28

Synthesis of 2-(3-fluoro-4-methoxyphenyl)-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 27(127mg, 0.38mmol) was reacted according to the same procedure as Preparation 23 to give 80mg(Yield 60%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.54(1H, d), 8.40-8.20(3H, m), 7.28(1H, m), 3.89(3H, s), 2.48(3H, s)

FAB MS(m/e) = 346[M^++1]

Preparation 29

Synthesis of 2-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 28(80mg, 0.23mmol) was dissolved in dichloromethane(10㎖), excess borontribromide was added thereto, and the resulting mixture was reacted for 2 hours at room temperature. The remaining borontribromide was decomposed by methanol and concentrated under reduced pressure. The solid thus produced was washed with dichloromethane to give 44mg(Yield 57%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.39((1H, s), 8.26(1H, s), 8.03(1H, d), 7.97 (1H, d), 7.13(1H, m), 2.41(3H, s)

FAB MS(m/e) = 332[M^++1]

Preparation 30

Synthesis of 3-(benzyloxy)-2-[4-(benzyloxy)-3-fluorophenyl]-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 29(30mg, 90μ mol) was reacted according to the same procedure as Preparation 24 to give 15.8mg(Yield 34%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.34(1H, s), 8.20(1H, s), 8.05(1H, d), 7.96(1H, d), 7.47-7.25(10H, m), 7.06(1H, m), 5.23(2H, s), 5.20(2H, s), 2.55(3H, s)

FAB MS(m/e) =512[M^++1]

Preparation 31

Synthesis of 8-amino-3-(benzyloxy)-2-[4-(benzyloxy)-3-fluorophenyl]-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 30(15mg, 29μ mol), 10 equivalents of iron and 3 drops of conc. hydrochloric acid were introduced into ethanol(5㎖) and then refluxed

for 1 hour. The reaction solution was concentrated, and the residue was dissolved in ethylacetate and filtered through a cellite pad to remove any insoluble substances. The organic extract was filtered through a silica gel pad and the filtrate was concentrated to give 10mg(Yield 71%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.19(1H, s), 8.06(1H, d), 7.50-7.28(12H, m), 7.10(1H, s), 6.86(1H, s), 5.64(2H, br s), 5.34(2H, s), 5.07(2H, s), 2.30(3H, s)

FAB MS(m/e) =482[M^++1]

Preparation 32

Synthesis of 2-{3-(benzyloxy)-2-[4-(benzyloxy)-3-fluorophenyl]-6-methyl-4-oxo-4*H*-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 31(10mg, 20μ mol) was reacted according to the same procedure as Preparation 26 to give 7mg(Yield 58%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.05(3H, m), 7.70-7.20(12H, m), 5.23(4H, m), 3.89(2H, t), 3.43(2H, t), 2.65(2H, m), 2.47(3H, s)

FAB MS(m/e) =586[M^++1]

Example 16

Synthesis of 2-[2-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 16)

The compound prepared in Preparation 32(5mg, 8.5μ mol) was reacted according to the same procedure as Example 15 to give 2.6mg(Yield 76%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.10(1H, d), 7.95(1H, d), 7.85(1H, s), 7.69(1H, s), 7.10(1H, m), 3.88(2H, t), 3.49(2H, t), 2.53(2H, m), 2.44(3H, s)

FAB MS(m/e) =406[M^++1]

Preparation 33

Synthesis of (*E*)-3-[4-(benzyloxy)-3-chlorophenyl]-1-(2-hydroxy-5-methyl-3-nitrophenyl)-2-propen-1-one

2-Hydroxy-5-methyl-3-nitroacetophenone(750mg, 3.84mmol) and 4-benzyloxy-3-chlorobenzaldehyde(1g, 3.84mmol) were reacted according to the same procedure as Preparation 15 to give 970mg(Yield 59%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.03(1H, s), 7.92(1H, s), 7.76(2H, m), 7.50-7.39 (7H, m), 7.00(1H, d), 5.23(2H, s), 2.42(3H, s)

FAB MS(m/e) =424[M^++1]

Preparation 34

Synthesis of 2-[4-(benzyloxy)-3-chlorophenyl]-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 33(970mg, 2.29mmol) was reacted according to the same procedure as Preparation 23 to give 590mg(Yield 59%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.41(1H, s), 8.38(1H, s), 8.27(1H, s), 8.21 (1H, d), 7.50-7.41(11H, m), 5.33(2H, s), 2.53(3H, s)

FAB MS(m/e) = 438[M^++1]

Preparation 35

Synthesis of 3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 34(590mg, 1.35mmol) was reacted according to the same procedure as Preparation 24 to give 340mg(Yield 47%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.43(1H, s), 8.28(1H, s), 8.20(1H, s), 8.05(1H, d),

7.49-7.31(11H, m), 5.33(2H, s), 5.16(2H, s), 2.53(3H, s)

FAB MS(m/e) = 528[M^++1]

Preparation 36

Synthesis of 8-amino-3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 35(100mg, 189μ mol) was reacted according to the same procedure as Preparation 31 to give 49.7mg(Yield 52%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.19(1H, s), 8.06(1H, d), 7.50-7.28(11H, m), 7.10(1H, s), 6.86(1H, s), 5.64(2H, br s), 5.34(2H, s), 5.07(2H, s), 2.30(3H, s)

FAB MS(m/e) = 498[M^++1]

Preparation 37

Synthesis of 2-{3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-6-methyl-4-oxo-4*H*-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 36(49.7mg, 100μ mol) was reacted according to the same procedure as Preparation 26 to give 49.4mg(Yield 82%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.20(1H, s), 8.10(1H, d), 7.90(1H, s), 7.73(1H, s), 7.51-7.30(11H, m), 5.32(2H, s), 5.10(2H, s), 3.86(2H, t), 3.47(2H, t), 2.50(2H, m), 2.46(3H, s)

FAB MS(m/e) = 602[M^++1]

Example 17

Synthesis of 2-[2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 17)

The compound prepared in Preparation 37(20mg, 33μ mol) was dissolved in dichloromethane solvent(5㎖), catalytic amount of 10% Pd/C was added thereto, and the resulting mixture was reacted under hydrogen pressure of 1atm for 10 hours. The reaction solution was filtered through a cellite pad and concentrated to give 8.2mg(Yield 58%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.30(1H, s), 8.08(1H, d), 7.86(1H, s), 7.67(1H, s), 7.11(1H, d), 3.88(2H, t), 3.49(2H, t), 2.54(2H, m), 2.45(3H, s)

FAB MS(m/e) = 422[M^++1]

Example 18

Synthesis of 2-[2-(3-bromo-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 18)

The compound prepared in Preparation 26(10mg, 15.5μ mol) was reacted with 1 equivalent of borontribromide according to the same procedure as Example 2 to give 5mg(Yield 69%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 11.0(1H, s), 9.68(1H, s), 8.45(1H, s), 8.13(1H, d), 7.87(1H, s), 7.70(1H, s), 7.11(1H, d), 3.88(2H, t), 3.50(2H, t), 2.53(2H, q), 2.49(3H, s)

FAB MS(m/e) = 466[M^++1]

Preparation 38

Synthesis of 2-(benzyloxy)-5-[3-(benzyloxy)-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-6-methyl-4-oxo-4*H*-chromen-2-yl]benzonitrile

The compound prepared in Preparation 26(164mg, 253μ mol) was dissolved in dimethylformamide(20㎖), bistribenzylidenedipalladium(10mg), diphenylphosphino-ferrocene(20mg) and zinc cyanide($ZnCN_2$; 149mg) were added thereto, and the resulting mixture was refluxed for 4 hours. After reaction, the solid was filtered out and the

solvent was removed. The residue was dissolved again in ethylacetate(50㎖), washed with water(50㎖), and then concentrated. The residue was purified by silica gel column chromatography(eluent: 75% ethylacetate/hexane) to give 50mg(Yield 33.4%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.30(1H, s), 8.24(1H, d), 8.04(1H, s), 7.60(1H, s), 7.46-7.22(10H, m), 7.01(1H, d), 5.28(2H, s), 5.11(2H, s), 3.82 (2H, t), 3.39(2H, t), 2.60(2H, q), 2.47(3H, s)

FAB MS(m/e) = 592[M^++1]

Example 19

Synthesis of 5-[8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-2-yl]-2-hydroxybenzonitrile(Compound 19)

The compound prepared in Preparation 38(10mg, 16.9μ mol) was reacted according to the same procedure as Example 15 except that the reaction was carried out under hydrogen pressure of 1 atm to give 6mg(Yield 86%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.30(1H, s), 8.07(1H, d), 7.83(1H, s), 7.63(1H, s), 6.58(1H, d), 3.87(2H, t), 3.48(2H, t), 2.55(2H, q), 2.43(3H, s)

FAB MS(m/e) =413[M^++1]

Preparation 39

Synthesis of (*E*)-3-[2,4-bis(benzyloxy)phenyl]-1-(2-hydroxy-5-methyl-3-nitrophenyl)-2-propen-1-one

2-Hydroxy-5-methyl-3-nitroacetophenone(500mg, 2.56mmol) and 2,4-dibenzyloxybenzaldehyde(900mg, 2.83mmol) were reacted according to the same procedure as Preparation 22 to give 540mg(Yield 43%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.10(1H, d), 7.93(1H, d), 7.72(1H, d), 7.57-7.30(13H, m), 5.13(2H, s), 5.11(2H, s), 2.22(3H, s)

FAB MS(m/e) =496[M^++1]

Preparation 40

Synthesis of 2-[2,4-bis(benzyloxy)phenyl]-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 39(540mg, 1.08mmol) was reacted according to the same procedure as Preparation 23 to give 480mg(Yield 87%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.34(1H, s), 8.14(1H, s), 7.70-7.20(11H, m), 6.73(2H, m), 6.46(1H, s), 5.12(2H, s), 5.08(2H, s), 2.53(3H, s)

FAB MS(m/e) = 510[M^++1]

Preparation 41

Synthesis of 3-(benzyloxy)-2-[2,4-bis(benzyloxy)phenyl]-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 40(480mg, 0.94mmol) was reacted according to the same procedure as Preparation 24 to give 436mg(Yield 77%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.39(1H, s), 8.13(1H, s), 7.60-7.13(16H, m), 6.64(2H, m), 5.14(2H, s), 5.10(2H, s), 5.00(2H, s), 2.58(3H, s)

FAB MS(m/e) = 600[M^++1]

Preparation 42

Synthesis of 8-amino-3-(benzyloxy)-2-[2,4-bis(benzyloxy)phenyl]-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 41(100mg, 166μ mol) was reacted

according to the same procedure as Preparation 31 to give 85mg(Yield 90%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 7.45-7.08(18H, m), 6.57(2H, m), 5.10-4.92(6H, m), 2.35(3H, s)

FAB MS(m/e) = 570[M^++1]

Preparation 43

Synthesis of 2-{3-(benzyloxy)-2-[2,4-bis(benzyloxy)phenyl]-6-methyl-4-oxo-4*H*-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 42(80mg, 140μ mol) was reacted according to the same procedure as Preparation 26 to give 70mg(Yield 74%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.03(1H, s), 7.60(1H, s), 7.44-7.02(16H, m), 6.62(2H, m), 5.10(2H, s), 5.04(2H, s), 4.88(2H, s), 3.55(2H, t), 3.12(2H, t), 2.49(3H, s), 2.28(2H, m)

FAB MS(m/e) = 674[M^++1]

Example 20

Synthesis of 2-[2-(2,4-dihydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 20)

The compound prepared in Preparation 43(50mg, 74μ mol) was reacted according to the same procedure as Example 15 except that the reaction was carried out under hydrogen pressure of 1 atm to give 26.2mg(Yield 87%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 9.76(1H, br s), 7.86(1H, s), 7.59(1H, s), 7.34(1H, d), 6.38(1H, s), 6.35(1H, d), 3.87(2H, m), 3.31(2H, m), 2.43(5H, m)

FAB MS(m/e) = 404[M^++1]

Preparation 44

Synthesis of (*E*)-3-(3-chloro-4-fluorophenyl)-1-(2-hydroxy-5-methyl-3-nitrophenyl)-2-propen-1-one

2-Hydroxy-5-methyl-3-nitroacetophenone(500mg, 2.56mmol) and 3-chloro-4-fluorobenzaldehyde(486mg, 3.07mmol) were reacted according to the same procedure as Preparation 22 to give 800mg(Yield 94%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.30-8.06(4H, m), 7.23(2H, m), 2.39(3H, s)

FAB MS(m/e) =336[M^++1]

Preparation 45

Synthesis of 2-(3-chloro-4-fluorophenyl)-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 44(800mg, 2.38mmol) was reacted according to the same procedure as Preparation 23 to give 600mg(Yield 72%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 11.70(1H, br s), 8.30-8.06(4H, m), 7.23(1H, m), 2.39(3H, s)

FAB MS(m/e) =350[M^++1]

Preparation 46

Synthesis of 2-(3-chloro-4-fluorophenyl)-3-methoxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 45(810mg, 2.31mmol) was reacted according to the same procedure as Preparation 24 except that iodomethane was used instead of benzyl bromide to give 750mg(Yield 89%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.32(1H, m), 8.24(1H, s), 8.18(1H, s), 8.13(1H, m), 7.24(1H, m), 3.87(3H, s), 2.48(3H, s)

FAB MS (m/e) = 364[M^++1]

Preparation 47

Synthesis of 8-amino-2-(3-chloro-4-fluorophenyl)-3-methoxy-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 46(200mg, 0.55mmol) was reacted according to the same procedure as Example 15 except that dichloromethane was used as the solvent instead of 10% methanol/dichloromethane to give 130mg(Yield 70%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.08(1H, d), 7.95(1H, m), 7.33(1H, s), 7.25(1H, m), 6.84(1H, s), 3.81(3H, s), 2.32(3H, s)

FAB MS (m/e) = 334[M^++1]

Preparation 48

Synthesis of 2-[2-(3-chloro-4-fluorophenyl)-3-methoxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 47(30mg, 90μ mol) was reacted according to the same procedure as Preparation 26 to give 21mg(Yield 53%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.29(1H, s), 8.14(1H, s), 8.03(1H, s), 7.61(1H, s), 7.25(2H, m), 3.88(3H, s), 3.84(2H, m), 3.41(2H, m), 2.63(2H, m), 2.46(3H, s)

FAB MS (m/e) = 438[M^++1]

Example 21

Synthesis of 2-[2-(3-chloro-4-fluorophenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 21)

The compound prepared in Preparation 48(21mg, 48μ mol) was reacted according

to the same procedure as Preparation 29 to give 16mg(Yield 78%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.38(1H, m), 8.24(1H, m), 8.01(1H, s), 7.66(1H, s), 7.35-7.25(2H, m), 3.89(2H, t), 3.44(2H, t), 2.67(2H, m), 2.48(3H, s)

FAB MS(m/e) =424[M^++1]

Preparation 49

Synthesis of (*E*)-3-[4-(benzyloxy)-3-methylphenyl]-1-(2-hydroxy-5-methyl-3-nitrophenyl)-2-propen-1-one

2-Hydroxy-5-methyl-3-nitroacetophenone(345mg, 1.76mmol) and 3-methyl-4-benzyloxybenzaldehyde(400mg, 1.76mmol) were reacted according to the same procedure as Preparation 22 to give 470mg(Yield 66%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.01(s, 1H), 7.93-7.86(2H, m), 7.53-7.38(10H, m), 6.93(1H, d), 5.15(2H, s), 2.42(3H, s), 2.32(3H, s)

FAB MS (m/e) = 404[M^++1]

Preparation 50

Synthesis of 2-[4-(benzyloxy)-3-methylphenyl]-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 49(470mg, 1.16mmol) was reacted according to the same procedure as Preparation 23 to give 420mg(Yield 83%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.33(1H, s), 8.22(3H, m), 7.46-7.33(5H, m), 7.15(1H, d), 6.90(1H, s), 5.19(2H, s), 2.56(3H, s), 2.39(3H, s)

FAB MS(m/e) =418[M^++1]

Preparation 51

Synthesis of 3-(benzyloxy)-2-[4-(benzyloxy)-3-methylphenyl]-6-methyl-8-

nitro-4*H*-chromen-4-one

The compound prepared in Preparation 50(420mg, 1.00mmol) was reacted according to the same procedure as Preparation 24 to give 380mg(Yield 74%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.35(1H, s), 8.18(1H, s), 8.10(2H, m), 7.46-7.29 (9H, m), 6.95(1H, d), 5.17(2H, s), 5.15(2H, s), 2.55(3H, s), 2.29(3H, s)

FAB MS(m/e) =508 [M^++1]

Preparation 52

Synthesis of 8-amino-3-(benzyloxy)-2-[4-(benzyloxy)-3-methylphenyl]-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 51(380mg, 749μ mol) was reacted according to the same procedure as Preparation 31 to give 330mg(Yield 92%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 7.79(2H, d), 7.45-7.30(8H, m), 6.93(1H, d), 6.83 (1H, s), 5.16(2H, s), 5.08(2H, s), 4.07(2H, br s), 2.37(3H, s), 2.29(3H, s)

FAB MS(m/e) = 478[M^++1]

Preparation 53

Synthesis of 2-{3-(benzyloxy)-2-[4-(benzyloxy)-3-methylphenyl]-6-methyl-4-oxo-4*H*-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 52(330mg, 691μ mol) was reacted according to the same procedure as Preparation 26 to give 370mg(Yield 92%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.05(1H, s), 7.93(2H, m), 7.65(1H, s), 7.50-7.20 (7H, m), 6.95(1H, d), 5.16(2H, s), 5.05(2H, s), 3.85(2H, t), 3.38(2H, t), 2.58(2H, m), 2.47(3H, s),

2.29(3H, s)

FAB MS (m/e) = 582[M^++1]

Example 22

Synthesis of 2-[3-hydroxy-2-(4-hydroxy-3-methylphenyl)-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 22)

The compound prepared in Preparation 53(370mg, 636μ mol) was reacted according to the same procedure as Example 15 to give 219mg(Yield 85.7%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 10.50(1H, br s), 9.40(1H, br s), 8.04(1H, s), 7.99(1H, d), 7.86(1H, s), 7.67(1H, s), 6.94(1H, d), 3.88(2H, t), 3.50(2H, t), 2.53(2H, m), 2.44(3H, s), 2.19(3H, s)

FAB MS (m/e) = 402 [M^++1]

Preparation 54

Synthesis of (*E*)-3-{4-(allyloxy)-3-[(allyloxy)methyl]phenyl}-1-(2-hydroxy-5-methyl-3-nitrophenyl)-2-propen-1-one

2-Hydroxy-5-methyl-3-nitroacetophenone(500mg, 2.56mmol) and 4-(allyloxy)-3-[(allyloxy)methyl]benzaldehyde(760mg, 3.27mmol) were reacted according to the same procedure as Preparation 22 to give 470mg(Yield 45%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.01(1H, s), 7.94(1H, s), 7.89(1H, d), 7.81(1H, s), 7.54(1H, d), 7.48(1H, d), 6.90(1H, d), 6.02(2H, m), 5.44-5.20(4H, m), 4.62(4H, s), 4.14(2H, d), 2.42(3H, s)

FAB MS(m/e) = 410[M^++1]

Preparation 55

Synthesis of 2-{4-(allyloxy)-3-[(allyloxy)methyl]phenyl}-3-hydroxy-6-methyl-

8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 54(470mg, 1.15mmol) was reacted according to the same procedure as Preparation 23 to give 296mg(Yield 61%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.50(1H, s), 8.33(1H, s), 8.30(1H, d), 8.24(1H, s), 7.02(1H, d), 6.91(1H, br s), 6.04(2H, m), 5.46-5.20(4H, m), 4.66(4H, m), 4.16(2H, d), 2.56(3H, s)

FAB MS (m/e) = 424[M^++1]

Preparation 56

Synthesis of 3-(allyloxy)-2-{4-(allyloxy)-3-[(allyloxy)methyl]phenyl}-6-methyl-8-nitro-4*H*-chromen-4-one

The compound prepared in Preparation 55(296mg, 0.699mmol) was reacted according to the same procedure as Preparation 24 except that allylbromide was used instead of benzylbromide to give 259mg(Yield 80%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.45(1H, s), 8.32(1H, s), 8.25(1H, d), 8.19(1H, s), 6.99(1H, d), 6.02(3H, m), 5.50-5.15(6H, m), 4.66(6H, m), 4.15(2H, d), 2.54(3H, s)

FAB MS(m/e) = 464 [M^++1]

Preparation 57

Synthesis of 3-(allyloxy)-2-{4-(allyloxy)-3-[(allyloxy)methyl]phenyl}-8-amino-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 56(259mg, 0.559mmol) was reacted according to the same procedure as Preparation 31 to give 150mg(Yield 61%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.13(1H, s), 8.04(1H, d), 7.39(1H, s), 6.95(1H, d),

6.82(1H, s), 6.07-5.90(3H, m), 5.50-5.10(6H, m), 4.76-4.60(6H, m), 4.13(2H, d), 2.36(3H, s)

FAB MS(m/e) = 434 [M^++1]

Preparation 58

Synthesis of 2-(3-(allyloxy)-2-{4-(allyloxy)-3-[(allyloxy)methyl]phenyl}-6-methyl-4-oxo-4*H*-chromen-8-yl)-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 57(150mg, 346μ mol) was reacted according to the same procedure as Preparation 26 to give 111mg(Yield 59%) of the title compound.

^{1}H NMR($CDCl_3$, ppm); δ 8.19(2H, s), 8.00(1H, s), 7.66(1H, d), 6.95(1H, d), 6.08-6.00(3H, m), 5.45-5.10(6H, m), 4.64-4.59(6H, m), 4.13(2H, s), 3.86(2H, t), 3.39(2H, t), 2.60(2H, m), 2.44(3H, s)

FAB MS(m/e) = 538 [M^++1]

Example 23

Synthesis of 2-{3-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]-6-methyl-4-oxo-4*H*-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione(Compound 23)

The compound prepared in Preparation 58(10mg, 18.6μ mol) was dissolved in 90% aqueous methanol solution, catalytic amount of p-toluenesulfonic acid and catalytic amount of 10% Pd/C were added thereto, and the resulting mixture was refluxed for 6 hours. The reaction mixture was filtered through a cellite and then concentrated. The residue was purified by silica gel column chromatography(eluent: 10% methanol/ methylene chloride) to give 2.4mg(Yield 30%) of the title compound.

^{1}H NMR(CD_3OD + $CDCl_3$, ppm); δ 8.04(1H, s), 8.02(1H, d), 7.83(1H, s), 7.52(1H, s), 6.82(1H, d), 4.67(2H, s), 3.81(2H, t), 3.36(2H, t), 2.56(2H, m), 2.34(3H, s)

FAB MS (m/e) = 418[M^++1]

Preparation 59

Synthesis of 2-{3-(benzyloxy)-2-[4-(benzyloxy)-3-(trifluoromethyl)phenyl]-6-methyl-4-oxo-4*H*-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 26(100mg, 155μ mol) was dissolved in dimethylformamide(5㎖), 2 equivalents of fluorosulfonyl(difluoromethyl)acetic acid methylester and catalytic amount of cuprous iodide(CuI) were added thereto, and the resulting mixture was reacted for 10 hours at 80℃. Water and ethylacetate were added and the mixture thus obtained was stirred. The organic layer was separated, filtered through a silica gel pad, and then concentrated to give 75mg(Yield 76%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.20(1H, s), 8.10(1H, d), 7.90(1H, s), 7.73 (1H, s), 7.51-7.30(11H, m), 5.32(2H, s), 5.10(2H, s), 3.86(2H, t), 3.47(2H, t), 2.50(2H, m), 2.46(3H, s)

FAB MS(m/e) = 636[M^++1]

Example 24

Synthesis of 2-[3-hydroxy-2-(4-hydroxy-3-(trifluoromethyl)phenyl)-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 24)

The compound prepared in Preparation 59(30mg, 47μ mol) was reacted according to the same procedure as Example 15 to give 19.7mg(Yield 91%) of the title compound.

^{1}H NMR(DMSO-d_6, ppm); δ 8.30(1H, s), 8.08(1H, d), 7.86(1H, s), 7.67 (1H, s), 7.11(1H, d), 3.88(2H, t), 3.49(2H, t), 2.54(2H, m), 2.45(3H, s)

FAB MS(m/e) = 456[M^++1]

Preparation 60

Synthesis of N-(4-methoxyphenyl)acetamide

Paraanisidine(136.34g, 1.108mol) was dissolved in dichloromethane(500㎖), triethylamine(234㎖, 1.66 mol) and acetic anhydride(114.8㎖, 1.22mol) were added thereto, and the resulting mixture was stirred for 1 hour. After completion of reaction, the reaction solution was concentrated. Water(800㎖) was added to the residue and the resulting mixture was stirred and filtered to give 168.0g(1.16mol, Yield 92%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 7.37(2H, d), 6.84(2H, d), 3.78(3H, s), 2.14(3H,s)

FAB MS(m/e)=166[M^++1]

Preparation 61

Synthesis of N-(3-acetyl-4-hydroxyphenyl)acetamide

The compound prepared in Preparation 60(167.44g, 1.014mol) and aluminum chloride(500g, 3.76mol) were mixed together in solid state, carbon disulfide(1340㎖) and acetylchloride(194㎖, 2.72mol) were added thereto, and the resulting mixture was stirred for 3 hours. After completion of reaction, water(800㎖) of 0℃ was added over about 30 minutes. The mixture thus obtained was extracted with dichloromethane(800㎖) and then extracted with 1N aqueous sodium hydroxide solution(700㎖). The aqueous layer was neutralized by 1N aqueous hydrochloric acid solution to give a solid having a yellow color. This solid was filtered and dried to give 130.6g(0.674mol, Yield 67%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 12.10(1H, s), 8.16(1H, d), 7.31(1H, dd), 7.17(1H, s), 6.93(1H, s), 2.62(3H, s), 2.18(3H, s)

FAB MS(m/e)=194[M^++1]

Preparation 62

Synthesis of N-(3-acetyl-4-hydroxy-5-nitrophenyl)acetamide

To the compound prepared in Preparation 61(120g, 0.62mol) was added acetic anhydride(1000㎖) and the mixture was cooled to 0℃. Dinitrocupper(107.2g, 0.442mol) was added thereto while a temperature of 0℃ was maintained and the resulting mixture was stirred for 2 hours. After completion of reaction, water(1L) of 0℃ was added and the resulting mixture was filtered and dried to give 90.4g(0.378mol, Yield 61%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.29(1H, s), 8.53(1H, s), 8.27(1H, s), 2.66(3H, s), 2.06(3H, s)

FAB MS(m/e)=239[M^++1]

Preparation 63

Synthesis of N-(3-{(E)-3-[4-(benzyloxy)phenyl]-2-propenoyl}-4-hydroxy-5-nitrophenyl)acetamide

The compound prepared in Preparation 62(32.3g, 0.135mol) was dissolved in 80% aqueous ethanol solution(600㎖), sodium hydroxide(16.3g, 0.406mol) and 4-benzyloxybenzaldehyde(34.5g, 0.163mol) were added thereto, and the resulting mixture was stirred for 24 hours. After completion of reaction, the reaction solution was neutralized by 1N aqueous hydrochloric acid solution. The yellow solid thus obtained was filtered, washed with water(300㎖) and methanol(200㎖), and then dried to give 53.2g(0.123mol, Yield 91%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.23(1H, s), 8.54(1H, s), 8.24(1H, s), 7.81-7.11(12H, m), 5.20(2H, s), 2.06(3H, s)

FAB MS(m/e)=433[M^++1]

Preparation 64

Synthesis of N-{2-[4-(benzyloxy)phenyl]-3-hydroxy-8-nitro-4-oxo-4H-chromen-6-yl}acetamide

The compound prepared in Preparation 63(45g, 0.104mol) was mixed with methanol(500mℓ), 10% aqueous sodium hydroxide solution(104mℓ, 0.260mol) and 30% aqueous hydrogen peroxide(50mℓ, 0.441mol) were added thereto, and the resulting mixture was stirred for 20 hours at room temperature. After completion of reaction, the reaction solution was neutralized by 1N aqueous hydrochloric acid solution. The yellow solid thus obtained was filtered, washed with water(300mℓ) and methanol(200mℓ), and then dried to give 24.3g (54.4mmol, Yield 52%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.58(1H, s), 8.78(1H, s), 8.64(1H, s), 8.25(2H, d), 7.49-7.37(6H, m), 7.24(2H, d), 5.21(2H, s), 2.11(3H, s)

FAB MS(m/e)=447[M^++1]

Preparation 65

Synthesis of N-{3-(benzyloxy)-2-[4-(benzyloxy)phenyl]-8-nitro-4-oxo-4H-chromen-6-yl}acetamide

The compound prepared in Preparation 64(23g, 51.5mmol) was dissolved in N,N-dimethylformamide(300mℓ), potassium carbonate(10.7g, 77.3mmol) and benzyl bromide(7.35mℓ, 61.8mmol) were added thereto, and the resulting mixture was stirred for 2 hours at room temperature. After completion of reaction, the reaction solution was concentrated. To the residue were added water(400mℓ) and methanol(100mℓ), which was then stirred for 30 minutes, filtered, washed with water(200mℓ) and methanol(100mℓ), and dried to give 26.8g(50.0mmol, Yield 97%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 8.80(1H, s), 8.61(1H, s), 8.10(2H, d), 7.46-7.31(10H, m), 7.20(2H, d), 5.20(2H, s), 5.10(2H, s), 2.12(3H, s)

FAB MS(m/e)=537[M^++1]

Preparation 66

Synthesis of N-{8-amino-3-(benzyloxy)-2-[4-(benzyloxy)phenyl]-4-oxo-4H-chromen-6-yl}acetamide

The compound prepared in Preparation 65(25.0g, 46.6mmol) was dissolved in dichloromethane(400mℓ) and ethanol(350mℓ), iron(26g, 466mmol) and conc. hydrochloric acid(10mℓ) were added thereto, and the resulting mixture was stirred under reflux for 7 hours. After completion of reaction, iron was filtered out and the filtrate was washed with dichloromethane(500mℓ) and concentrated. Methanol(200mℓ) was added to the residue and the resulting mixture was stirred and filtered to give 17.3g(34.1mmol, Yield 73%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 8.12(2H, d), 7.48-7.29(12H, m), 7.13(2H, d), 5.22(2H, s), 5.04(2H, s), 2.05(3H, s)

FAB MS(m/e)=507[M^++1]

Preparation 67

Synthesis of N-{3-(benzyloxy)-2-[4-(benzyloxy)phenyl]-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-4-oxo-4H-chromen-6-yl}acetamide

The compound prepared in Preparation 66(16g, 31.6mmol) was dissolved in dichloromethane(300mℓ), triethylamine(22mℓ, 158mmol), 3-chloropropanesulfonylchloride (28g, 158mmol) and N,N-dimethylaminopyridine(100mg, 0.81mmol) were added thereto, and the resulting mixture was stirred for 1 hour at room temperature. After reaction was completed, the reaction solution was concentrated. To the residue were added N,N-dimethylformamide(300mℓ) and 2N aqueous sodium hydroxide solution(200mℓ, 400mmol) and the resulting mixture was stirred for 2 hours while heated to about 60℃. After completion of reaction, water(400mℓ) was added and stirred at room temperature. The yellow solid thus obtained was filtered, washed with methanol(200mℓ), and then dried to give 18.3g(30mmol, Yield 95%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.50(1H, s), 8.08(2H, d), 8.01(1H, s), 7.46-7.23(10H, m), 7.02(2H, d), 5.13(2H, d), 5.01(2H, d), 3.88(2H, t), 3.33(2H, t), 2.59(2H, quin), 2.97(3H, s)

FAB MS(m/e)=611[M^++1]

Preparation 68

Synthesis of 2-{6-amino-3-(benzyloxy)-2-[4-(benzyloxy)phenyl]-4-oxo-4H-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 67(15g, 24.6mmol) was dissolved in dichloromethane(200㎖) and methanol(200㎖), 2N aqueous sodium hydroxide solution(100㎖) was added thereto, and the resulting mixture was stirred under reflux for 1 hour. After completion of reaction, the reaction solution was concentrated. To the residue was added water(200㎖), which was then neutralized by 1N aqueous hydrochloric acid solution. The yellow solid thus obtained was filtered, washed with water(200㎖) and methanol(100㎖), and then dried to give 13.2g(23.2mmol, Yield 94%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 7.98(2H, d), 7.45-7.20(10H, m), 7.02(2H, d), 5.13(2H, s), 5.02(2H, s), 3.90(2H, s), 3.83(2H, t), 3.37(2H, t), 2.55(2H, quin)

FAB MS(m/e)=569[M^++1]

Preparation 69

Synthesis of 2-{6-anilino-3-(benzyloxy)-2-[4-(benzyloxy)phenyl]-4-oxo-4H-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 68(110mg, 0.193mmol), iodobenzene (197mg, 0.967mmol), sodium tert-butoxide(93mg, 0.967mmol), palladium dibenzylidene-acetone(35mg, 0.039mmol) and binap(30mg, 0.039mmol) were mixed, toluene(20㎖) was added thereto, and the resulting mixture was stirred under reflux for 2 hours. After completion of reaction, the solid was filtered out and the filtrate was washed with water(30 ㎖x2). The resulting solution was concentrated and the residue was purified by column chromatography(eluent: ethylacetate/n-hexane=1/1, v/v) to give 78mg(0.12mmol, Yield

63%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.01(2H, d), 7.82(1H, d), 7.52(1H, d), 7.45-7.24(12H, m), 7.15(2H, d), 7.04-7.02(3H, m), 5.93(1H, s), 5.14(2H, s), 5.03(2H, s), 3.85(2H, t), 3.37(2H, t), 2.56(2H, quin)

FAB MS(m/e)=645[M^++1]

Preparation 70

Synthesis of t-butyl acetyl [3-(benzyloxy)-2-[4-(benzyloxy)phenyl]-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-4-oxo-4H-chromen-6-yl]carbamate

The compound prepared in Preparation 67(1.0g, 1.64mmol) was dissolved in dichloromethane(70㎖), di-t-butoxydicarbonyl(394mg, 1.84mmol) and N,N-dimethyl-aminopyridine(30mg, 0.245mmol) were added thereto, and the resulting mixture was stirred for 2 hours at room temperature. After completion of reaction, the reaction solution was concentrated. To the residue was added water(80㎖), which was then stirred, filtered, washed with methanol(20㎖) and dried to give 1.13g(1.58mmol, Yield 97%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.02(2H, d), 7.99(1H, s), 7.56(1H, s), 7.47-7.26(10H, m), 7.04(2H, d), 5.14(2H, s), 5.06(2H, s), 3.86(2H, t), 3.37(2H, t), 2.65(3H, s), 2.57(2H, quin), 1.49(9H, s)

FAB MS(m/e)=711[M^++1]

Preparation 71

Synthesis of t-butyl 3-(benzyloxy)-2-[4-(benzyloxy)phenyl]-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-4-oxo-4H-chromen-6-ylcarbamate

The compound prepared in Preparation 70(1.10g, 1.55mmol) was dissolved in dichloromethane(70㎖) and methanol(70㎖), 2N aqueous sodium hydroxide solution(40㎖, 80mmol) was added thereto, and the resulting mixture was stirred under reflux for 1 hour.

After completion of reaction, the reaction solution was concentrated. To the residue was added water(100㎖), which was then neutralized by 1N aqueous hydrochloric acid solution, filtered, washed with water(50㎖) and methanol(20㎖) and dried to give 950mg(1.42mmol, Yield 92%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.07(1H, s), 8.05(2H, d), 8.01(1H, s), 7.88(1H, s), 7.45-7.26(10H, m), 7.03(2H, d), 5.13(2H, s), 5.02(2H, s), 3.87(2H, t), 3.37(2H, t), 2.57(2H, quin), 1.51(9H, s)

FAB MS(m/e)=669[M^++1]

Preparation 72

Synthesis of t-butyl 3-(benzyloxy)-2-[4-(benzyloxy)phenyl]-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-4-oxo-4H-chromen-6-yl(methyl)carbamate

The compound prepared in Preparation 71(450mg, 0.67mmol) was dissolved in tetrahydrofuran(50㎖), sodium hydride(54mg, 60%, 1.34mmol) and iodomethane(3㎖, 48.2mmol) were added thereto, and the resulting mixture was stirred for 1 hour at room temperature. After completion of reaction, methanol(10㎖) was added to the reaction solution and concentrated. To the residue was added water(50㎖), which was then stirred, filtered and dried to give 440mg(0.64mmol, Yield 96%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.03(2H, d), 7.45-7.26(12H, m), 7.04(2H, d), 5.14(2H, s), 5.04(2H, s), 3.86(2H, t), 3.37(2H, t), 3.34(3H, s), 2.57(2H, quin), 1.50(9H, s)

FAB MS(m/e)=683[M^++1]

Preparation 73

Synthesis of 2-[3-(benzyloxy)-2-[4-(benzyloxy)phenyl]-6-(methylamino)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione

To the compound prepared in Preparation 72(200mg, 0.29mmol) were added dichloromethane(15㎖) and trifluoroacetic acid(8㎖), and the resulting mixture was stirred

for 1 hour at room temperature. After reaction was completed, the reaction solution was concentrated. To the residue was added diethylether(40㎖), and the resulting mixture was stirred, filtered, washed with methanol(20㎖) and dried to give 155mg(0.266mmol, Yield 92%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.02(2H, d), 7.46-7.26(12H, m), 7.02(2H, d), 5.13(2H, s), 5.05(2H, s), 3.86(2H, t), 3.37(2H, t), 3.34(3H, s), 2.57(2H, quin)

FAB MS(m/e)=583[M^++1]

Preparation 74

Synthesis of 2-{3-(benzyloxy)-6-{[2-(benzyloxy)ethyl]amino}-2-[4-(benzyloxy)phenyl]-4-oxo-4H-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 68(54mg, 0.094mmol) was dissolved in dichloroethane(15㎖), benzyloxyacetaldehyde(47mg, 0.32mmol) and sodium triacetoxyborohydride(64mg, 0.30mmol) were added thereto, and the resulting mixture was stirred for 1 hour at room temperature. After completion of reaction, the reaction solution was washed with water(20㎖x2) and concentrated. The residue was purified by column chromatography(eluent: ethylacetate/n-hexane=1/1, v/v) to give 59mg(0.084mmol, Yield 89%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.00(2H, d), 7.46-7.24(16H, m), 7.13(1H, s), 7.02(2H, d), 5.13(2H, s), 5.03(2H, s), 4.56(2H, s), 4.33(1H, t), 3.80(2H, t), 3.74(2H, t), 3.40(2H, t), 3.36(2H, t), 2.54(2H, quin)

FAB MS(m/e)=703[M^++1]

Preparation 75

Synthesis of 3-chloro-4-hydroxybenzaldehyde

Acetic acid(300㎖) was bubbled with chlorine gas to make 38.38g(0.541mol) of chlorine. 4-Hydroxybenzaldehyde(66.1g, 0.541mol) was dissolved in acetic acid(300㎖)

and stirred, during which the acetic acid solution containing chlorine as prepared above was slowly added thereto over 2 hours. The resulting mixture was stirred for further 2 hours. After completion of reaction, the reaction solution was concentrated. To the residue was added water(1L), which was then filtered, washed with water(500㎖) and dried to give 63.16g(0.403mol, Yield 75%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); 9.84(1H, s), 7.89(1H, s), 7.74(1H, d), 7.15(1H, d), 6.17(1H, s)

FAB MS(m/e)=157[M^++1]

Preparation 76

Synthesis of 4-(benzyloxy)-3-chlorobenzaldehyde

The compound prepared in Preparation 75(63.16g, 0403mol) was dissolved in N,N-dimethylformamide(300㎖), potassium carbonate(72.4g, 0.524mol) and benzyl bromide(53㎖, 0.443mol) were added thereto, and the resulting mixture was stirred for 4 hours at room temperature. After completion of reaction, the reaction solution was concentrated. To the residue was added water(500㎖), which was then filtered, washed with water(200㎖) and n-hexane(100㎖), and dried to give 88.56g(0.359mol, Yield 89%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 9.84(1H, s), 7.93(1H, s), 7.71(1H, d), 7.46-7.32(5H, m), 7.07(1H, d), 5.26(3H, s)

FAB MS(m/e)=247[M^++1]

Preparation 77

Synthesis of N-(3-{(E)-3-[4-(benzyloxy)-3-chlorophenyl]-2-propenyl}-4-hydroxy-5-nitrophenyl)acetamide

The compound prepared in Preparation 62(30.0g, 0.126mol) was dissolved in 80% aqueous ethanol solution(600㎖), sodium hydroxide(16.3g, 0.406mol) and the compound

prepared in Preparation 76(38.5g, 0.156mol) were added thereto, and the resulting mixture was stirred for 24 hours. After completion of reaction, the reaction solution was neutralized by 1N aqueous hydrochloric acid solution. The yellow solid thus obtained was filtered, washed with water(400㎖) and methanol(200㎖), and dried to give 52.2g (0.112mol, Yield 89%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 12.23(1H, s), 10.24(1H, s), 8.52(1H, s), 8.21(1H, s), 8.05(1H, s), 7.79-7.34(9H, m), 5.30(2H, s), 2.08(3H, s)

FAB MS(m/e)=467[M^++1]

Preparation 78

Synthesis of N-{2-[4-(benzyloxy)-3-chlorophenyl]-3-hydroxy-8-nitro-4-oxo-4H-chromen-6-yl}acetamide

The compound prepared in Preparation 77(50g, 0.107mol) was mixed with methanol(600㎖), 10% aqueous sodium hydroxide solution(104㎖, 0.260mol) and 30% aqueous hydrogen peroxide(50㎖, 0.441mol) were added thereto, and the resulting mixture was stirred for 20 hours at room temperature. After reaction was completed, the reaction solution was neutralized by 1N aqueous hydrochloric acid solution. The yellow solid thus obtained was filtered, washed with water(350㎖) and methanol(250㎖), and dried to give 26.2g (54.5mmol, Yield 51%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.56(1H, s), 8.78(1H, s), 8.64(1H, s), 8.23(1H, s), 7.92(1H, d), 7.49-7.37(6H, m), 7.22(1H, d), 5.23(2H, s), 2.10(3H, s)

FAB MS(m/e)=481[M^++1]

Preparation 79

Synthesis of N-{3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-8-nitro-4-oxo-4H-chromen-6-yl}acetamide

The compound prepared in Preparation 78(24g, 49.9mmol) was dissolved in

dimethylformamide(300㎖), potassium carbonate(10.7g, 77.3mmol) and benzylbromide (7.35㎖, 61.8mmol) were added thereto, and the resulting mixture was stirred for 2 hours at room temperature. After completion of reaction, the reaction solution was concentrated. To the residue were added water(400㎖) and methanol(100㎖), and then the mixture thus obtained was stirred for 30 minutes, filtered, washed with water(200㎖) and methanol(100 ㎖), and dried to give 27.3g(47.8mmol,Yield 96%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.56(1H, s), 8.78(1H, s), 8.64(1H, s), 8.23(1H, s), 7.92(1H, d), 7.49-7.29(10H, m), 7.22(1H, d), 5.23(2H, s), 5.10(2H, s), 2.10(3H, s)

FAB MS(m/e)=571[M^++1]

Preparation 80

Synthesis of N-{8-amino-3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-4-oxo-4H-chromen-6-yl}acetamide

The compound prepared in Preparation 79(26.0g, 45.5mmol) was dissolved in dichloromethane(400㎖) and ethanol(350㎖), iron(26g, 466mmol) and conc. hydrochloric acid(10㎖) were added thereto, and the resulting mixture was stirred under reflux for 6 hours. After completion of reaction, iron was filtered out, and then the filtrate was washed with dichloromethane(500㎖) and concentrated. To the residue was added methanol(200㎖), which was then stirred and filtered to give 18.3g(33.8mmol, Yield 74%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.03(1H, s), 8.20(1H, s), 8.08(1H, d), 7.45-7.29(13H, s), 5.82(2H, s), 5.34(2H, s), 5.07(2H, s), 2.05(3H, s)

FAB MS(m/e)=541[M^++1]

Preparation 81

Synthesis of N-{3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-8-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-4-oxo-4H-chromen-6-yl}acetamide

The compound prepared in Preparation 80(17g, 31.4mmol) was dissolved in dichloromethane(300㎖), triethylamine(22㎖, 158mmol), 3-chloropropanesulfonylchloride (28g, 158mmol) and N,N-dimethylaminopyridine(100mg, 0.81mmol) were added thereto, and the resulting mixture was stirred for 1 hour at room temperature. After reaction was completed, and reaction solution was concentrated. To the residue were added N,N-dimethylformamide(300㎖) and 2N aqueous sodium hydroxide solution(200㎖, 400mmol), which was then stirred for 2 hours while heated to about 60℃. After completion of reaction, water(400㎖) was added and the resulting solution was stirred at room temperature. The yellow solid thus obtained was filtered, washed with methanol(200㎖), and dried to give 18.7g(29.0mmol, Yield 92%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.53(1H, s), 8.22(1H, s), 8.07(1H, s), 8.01(1H, d), 7.48-7.24(10H, m), 7.00(1H, d), 5.22(2H, s), 5.04(2H, s), 3.89(2H, t), 3.38(2H, t), 2.61(2H, quin), 2.17(3H, s)

FAB MS(m/e)=645[M^++1]

Preparation 82

Synthesis of 2-{6-amino-3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-4-oxo-4H-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 81(12g, 18.6mmol) was dissolved in dichloromethane(150㎖) and methanol(150㎖), 2N aqueous sodium hydroxide solution(100㎖) was added thereto, and the resulting mixture was stirred under reflux for 1 hour. After reaction was completed, the reaction solution was concentrated. To the residue was added water(200㎖), which was then neutralized by 1N aqueous hydrochloric acid solution. The yellow solid thus obtained was filtered, washed with water(200㎖) and methanol(100㎖), and dried to give 10.4g(17.2mmol, Yield 93%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.10(1H, s), 7.96(1H, d), 7.48-7.19(12H, m), 6.99(1H, d), 5.23(2H, s), 5.06(2H, s), 3.91(2H, s), 3.81(2H, t), 3.38(2H, t), 2.58(2H, quin)

FAB MS(m/e)=603[M^++1]

Preparation 83

Synthesis of 2-{3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-6-(dimethylamino)-4-oxo-4H-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione

The compound prepared in Preparation 82(500mg, 0.829mmol) was dissolved in acetone(70㎖), potassium carbonate(300mg, 2.17mmol) and iodomethane(5㎖, 80.3mmol) were added thereto, and the resulting mixture was stirred under reflux for 3 hours. After completion of reaction, the reaction solution was concentrated. To the residue was added water(50㎖), which was then stirred, filtered, and dried to give 495mg(0.784mmol, Yield 95%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 8.19(1H, s), 8.04(1H, d), 7.48-7.30(12H, m), 6.99(1H, d), 5.32(2H, s), 5.06(2H, s), 3.88(2H, t), 3.39(2H, t), 3.01(6H, s), 2.58(2H, quin)

FAB MS(m/e)=631[M^++1]

Preparation 84

Synthesis of t-butyl acetyl [3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-4-oxo-4H-chromen-6-yl]carbamate

The compound prepared in Preparation 81(1.05g, 1.63mmol) was dissolved in dichloromethane(70㎖), di-t-butyloxydicarbonyl(394mg, 1.84mmol) and N,N-dimethyl-aminopyridine(30mg, 0.245mmol) were added thereto, and the resulting mixture was stirred for 2 hours at room temperature. After completion of reaction, the reaction solution was concentrated. To the residue was added water(80㎖), which was then stirred, filtered, washed with methanol(20㎖), and dried to give 1.15g(1.54mmol, Yield 95%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.12(1H, s), 7.98-7.96(2H, m), 7.58(1H, s), 7.48-7.24(10H, m), 7.00(1H, d), 5.24(2H, s), 5.11(2H, s), 3.85(2H, t), 3.39(2H, t), 2.65(3H, s), 2.60(2H, quin), 1.40(9H, s)

FAB MS(m/e)=745[M^++1]

Preparation 85

Synthesis of t-butyl 3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-4-oxo-4H-chromen-6-ylcarbamate

The compound prepared in Preparation 84(1.10g, 1.48mmol) was dissolved in dichloromethane(70㎖) and methanol(70㎖), 2N aqueous sodium hydroxide solution(40㎖, 80mmol) was added thereto, and the resulting mixture was stirred under reflux for 1 hour. After completion of reaction, the reaction solution was concentrated. To the residue was added water(100㎖), which was then neutralized by 1N aqueous hydrochloric acid solution, filtered, washed with water(50㎖) and methanol(20㎖), and dried to give 980mg(1.39mmol, Yield 94%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.19(1H, s), 8.00-7.98(2H, m), 7.48-7.24(11H, m), 6.99(1H, d), 5.24(2H, s), 5.07(2H, s), 3.86(2H, t), 3.39(2H, t), 2.60(2H, quin), 1.40(9H, s)

FAB MS(m/e)=703[M^++1]

Preparation 86

Synthesis of t-butyl 3-(benzyloxy)-2-[4-(benzyloxy)-3-chlorophenyl]-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-4-oxo-4H-chromen-6-yl(methyl)carbamate

The compound prepared in Preparation 85(900mg, 1.28 mmol) was dissolved in tetrahydrofuran(80㎖), sodium hydride(102mg, 60%, 2.56mmol) and iodomethane(3㎖, 48.2mmol) were added thereto, and the resulting mixture was stirred for 1 hour at room temperature. After completion of reaction, methanol(10㎖) was added and the resulting mixture was concentrated. To the residue was added water(50㎖), which was then stirred, filtered, and dried to give 870mg(1.21mmol, Yield 95%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm); δ 8.15(1H, s), 8.02-7.99(2H, m), 7.49-7.24(11H, m), 7.00(1H, d), 5.24(2H, s), 5.08(2H, s), 3.85(2H, t), 3.40(2H, t), 3.34(3H, s), 2.60(2H, quin),

1.40(9H, s)

FAB MS(m/e)=717[M^++1]

Preparation 87

Synthesis of t-butyl 2-(3-chloro-4-hydroxyphenyl)-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-3-hydroxy-4-oxo-4H-chromen-6-yl(methyl)carbamate

The compound prepared in Preparation 86(800mg, 1.11mmol) was dissolved in 10% methanol/dichloromethane solution(50㎖), 10% palladium/carbon(50mg) was added thereto, and hydrogenation reaction was carried out under atmospheric pressure. After completion of reaction, palladium/carbon was filtered out and the filtrate was concentrated. To the residue was added dichloromethane(50㎖), which was then stirred and filtered to give 420mg(0.782mmol, Yield 70%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 8.30(1H, s), 8.07(1H, d), 7.88(1H, s), 7.81(1H, s), 7.08(1H, s), 3.89(2H, t), 3.50(2H, t), 3.16(3H, s), 2.54(2H, quin), 1.42(9H, s)

FAB MS(m/e)=537[M^++1]

Example 25

Synthesis of 2-[6-amino-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 25)

The compound prepared in Preparation 68(3.0g, 5.28mmol) was dissolved in methanol(200㎖) and dichloromethane(100㎖), 10% palladium/carbon(200mg) was added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 2 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue was added dichloromethane(50㎖), which was then stirred and filtered to give 1.85g(4.76mmol, Yield 90%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.05(1H, s), 9.11(1H, s), 8.06(2H, d), 7.18(1H, s), 6.94(1H, s), 6.90(2H, s), 6.12(2H, s), 3.84(2H, t), 3.49(2H, t), 2.51(2H, quin)

FAB MS(m/e)=389[M^++1]

Example 26

Synthesis of 2-[6-(dimethylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 26)

The compound prepared in Preparation 68(200mg, 0.352mmol) was dissolved in methanol(30㎖) and dichloromethane(30㎖), formalin(1.0㎖, 13.3mmol) and 10% palladium/carbon(30mg) were added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 2 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue was added dichloromethane(30㎖), which was then stirred and filtered to give 102mg(0.244mmol, Yield 70%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); 10.07(1H, s), 9.18(1H, s), 8.10(2H, d), 7.30(1H, s), 7.09(1H, s), 7.92(2H, d), 3.89(2H, t), 3.50(2H, t), 3.00(6H, s), 2.50(2H, quin)

FAB MS(m/e)=417[M^++1]

Example 27

Synthesis of 2-[6-(diethylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 27)

The compound prepared in Preparation 68(100mg, 0.176mmol) was dissolved in ethanol(20㎖) and dichloromethane(20㎖), acetaldehyde(0.5㎖, 8.94mmol) and 10% palladium/carbon(20mg) were added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 3 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue was added dichloromethane(20㎖), which was then stirred and filtered to give 51mg(0.115mmol, Yield 65%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 8.00(2H, d), 7.45(1H, s), 7.19(1H, s), 7.04(2H, d),

3.86(2H, t), 3.43(4H, q), 3.37(2H, t), 2.56(2H, quin), 1.20(6H, t)

FAB MS(m/e)=445[M^++1]

Example 28

Synthesis of 2-[6-(benzylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 28)

The compound prepared in Preparation 68(150mg, 0.264mmol) was dissolved in methanol(30㎖) and dichloromethane(30㎖), benzaldehyde(1.0㎖, 9.83mmol) and 10% palladium/carbon(30mg) were added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 2 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue was added dichloromethane(30㎖), which was then stirred and filtered to give 84mg(0.175mmol, Yield 66%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.08(1H, s), 9.05(1H, s), 8.05(2H, d), 7.40-7.15(6H, m), 6.93(1H, s), 6.90(2H, d), 6.77(1H, t), 4.35(2H, d), 3.83(2H, t), 3.42(2H, t), 2.62(2H, quin)

FAB MS(m/e)=479[M^++1]

Example 29

Synthesis of 2-[3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-6-(4-piperidinylamino)-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 29)

The compound prepared in Preparation 68(350mg, 0.615mmol) was dissolved in methanol(50㎖) and dichloromethane(50㎖), 1-t-butoxy-4-piperidone(500mg, 2.5mmol), acetic acid(0.1㎖) and 10% palladium/carbon(20mg) were added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 4 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue were added dichloromethane(20㎖) and trifluoroacetic acid(10㎖), which

was then stirred for 1 hour at room temperature. After completion of reaction, diethylether(30㎖) was added, stirred, filtered, washed with dichloromethane(20㎖), and dried to give 121mg(0.256mmol, Yield 42%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 8.05(2H, d), 7.19(1H, s), 6.96(1H, s), 6.90(2H, d), 6.08(1H, d), 3.83(2H, t), 3.48(2H, t), 3.36-3.31(3H, m), 2.98(2H, q), 2.62(2H, quin), 1.90(2H, q), 1.29(2H, q)

FAB MS(m/e)=472[M^++1]

Example 30

Synthesis of 2-[6-(cyclohexylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 30)

The compound prepared in Preparation 68(200mg, 0.352mmol) was dissolved in methanol(30㎖) and dichloromethane(30㎖), cyclohexanone(1.0㎖, 9.65mmol), acetic acid(0.1㎖) and 10% palladium/carbon(30mg) were added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 7 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. The residue was purified by column chromatography(eluent: methanol/dichloromethane=9/1, v/v) to give 77mg(0.163mmol, Yield 46%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.07(1H, s), 9.09(1H, s), 8.05(2H, d), 7.18(1H, s), 6.94-6.90(3H, m), 6.04(1H, d), 3.85(2H, t), 3.48(2H, t), 3.32(1H, quin), 2.52(2H, quin), 1.97(2H, q), 1.75(2H, q), 1.38-1.18(6H, m)

FAB MS(m/e)=471[M^++1]

Example 31

Synthesis of 2-[6-anilino-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 31)

The compound prepared in Preparation 69(70mg, 0.108mmol) was dissolved in

methanol(10㎖) and dichloromethane(10㎖), 10% palladium/carbon(15mg) was added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 2 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue was added dichloromethane(20㎖), which was then stirred and filtered to give 43mg(0.093mmol, Yield 86%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 8.06(1H, s), 7.78(2H, d), 7.25-7.02(5H, m), 6.82-6.80(3H, m), 3.82(2H, t), 3.51(2H, t), 2.50(2H, quin)

FAB MS(m/e)=465 [M^++1]

Example 32

Synthesis of 2-[3-hydroxy-2-(4-hydroxyphenyl)-6-(methylamino)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 32)

The compound prepared in Preparation 73(85mg, 0.146mmol) was dissolved in methanol(15㎖) and dichloromethane(15㎖), 10% palladium/carbon(20mg) was added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 2 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue was added dichloromethane(20㎖), which was then stirred and filtered to give 48mg(0.119mmol, Yield 82%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.02(1H, s), 9.20(1H, s), 8.12(2H, d), 7.31(1H, s), 7.07(1H, s), 7.91(2H, d), 6.18(1H, q), 3.88(2H, t), 3.51(2H, t), 3.00(3H, s), 2.50(2H, quin)

FAB MS(m/e)=403[M^++1]

Example 33

Synthesis of 2-{3-hydroxy-6-[(2-hydroxyethyl)(methyl)amino]-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione(Compound 33)

The compound prepared in Preparation 74(50mg, 0.0711mmol) was dissolved in methanol(10㎖) and dichloromethane(10㎖), formalin(0.5㎖) and 10% palladium/carbon

(10mg) were added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 2 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue was added dichloromethane(20㎖), which was then stirred and filtered to give 21mg(0.0470mmol, Yield 66%) of the title compound.

^{1}H NMR (CD_3OD, ppm); δ 8.18(2H, d), 7.38(1H, s), 7.26(1H, s), 6.91(2H, d), 3.92(2H, t), 3.76(2H, t), 3.55(2H, t), 3.47(2H, t), 3.08(3H, s), 2.63(2H, quin)

FAB MS(m/e)=447[M^++1]

Example 34

Synthesis of N-[2-(3-chloro-4-hydroxyphenyl)-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-3-hydroxy-4-oxo-4H-chromen-6-yl]acetamide(Compound 34)

The compound prepared in Preparation 81(100mg, 0.155mmol) was dissolved in methanol(4㎖) and dichloromethane(36㎖), 10% palladium/carbon(30mg) was added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 2 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue was added dichloromethane(30㎖), which was then stirred and filtered to give 58mg(0.124mmol, Yield 80%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 11.03(1H, s), 10.59(1H, s), 10.07(1H, s), 8.23(1H, s), 7.99(1H, d), 7.20(1H, s), 7.05(1H, d), 6.92(1H, s), 3.82(2H, t), 3.39(2H, t), 2.43(2H, quin), 2.12(3H, s)

FAB MS(m/e)=465[M^++1]

Example 35

Synthesis of 2-[6-amino-2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 35)

The compound prepared in Preparation 82(100mg, 0.166mmol) was dissolved in methanol(4㎖) and dichloromethane(36㎖), 10% palladium/carbon(30mg) was added

thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 2 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue was added dichloromethane(30㎖), which was then stirred and filtered to give 62mg(0.146mmol, Yield 88%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); δ 10.90(1H, s), 9.37(1H, s), 8.23(1H, s), 8.05(1H, d), 7.14-7.11(3H, m), 5.60(2H, s), 3.81(2H, t), 3.48(2H, t), 2.49(2H, quin)

FAB MS(m/e)=423[M^++1]

Example 36

Synthesis of 2-[2-(3-chloro-4-hydroxyphenyl)-6-(dimethylamino)-3-hydroxy-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 36)

The compound prepared in Preparation 83(450mg, 0.713mmol) was dissolved in methanol(10㎖) and dichloromethane(90㎖), 10% palladium/carbon(60mg) was added thereto, and hydrogenation reaction was carried out using a balloon. After stirring for 2 hours to complete the reaction, palladium/carbon was filtered out, and the filtrate was concentrated. To the residue was added dichloromethane(80㎖), which was then stirred and filtered to give 285mg(0.632mmol, Yield 89%) of the title compound.

^{1}H NMR (CD_3OD, ppm); δ 8.33(1H, s), 8.13(1H, d), 7.38(1H, s), 7.27(1H, s), 7.01(1H, d), 3.92(2H, t), 3.64(2H, t), 3.05(6H, s), 2.65(2H, quin)

FAB MS(m/e)=451[M^++1]

Example 37

Synthesis of 2-[2-(3-chloro-4-hydroxyphenyl)-6-(methylamino)-3-hydroxy-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 37)

The compound prepared in Preparation 87(410mg, 0.764mmol) was dissolved in dichloromethane(15㎖) and trifluoroacetic acid(10㎖) and the resulting mixture was stirred for 2 hours at room temperature. After completion of reaction, the reaction solution was

concentrated. To the residue was added diethylether(30㎖), which was then stirred, filtered, washed with dichloromethane(30㎖), and dried to give 323mg(0.739mmol, Yield 97%) of the title compound.

^{1}H NMR (DMSO-D_6, ppm); 8.20(1H, s), 7.99(1H, d), 7.16(1H, s), 7.02(1H, d), 6.90(1H, s), 6.20(1H, q), 3.90(2H, t), 3.38(2H, t), 2.99(3H, d), 2.52(2H, quin)

FAB MS(m/e)=437[M^++1]

Preparation 88

Synthesis of (*E*)-1-(3-bromo-2-hydroxy-5-methylphenyl)-3-(3-chloro-4-methoxyphenyl)-2-propen-1-one

1-(3-Bromo-2-hydroxy-5-methylphenyl)-1-ethanone(10g, 43.7mmol) and 3-chloro-4-methoxybenzaldehyde(9.0g, 1.2몰당량) were introduced into 80% aqueous ethanol solution(150㎖), sodium hydroxide(NaOH; 5.2g, 3.0molar eq.) was added thereto, and the resulting mixture was stirred for 17 hours at room temperature. After completion of reaction, the reaction solution was neutralized by 2N aqueous hydrochloric acid solution and diluted with water(150㎖). The yellow solid thus precipitated was washed with water and methanol to give 14.2g (Yield 85%) of the purified title compound.

^{1}H NMR ($CDCl_3$, ppm) : 7.88(1H, d), 7.78(1H, s), 7.68(1H, s), 7.63(1H, s), 7.54(2H, m), 6.87(1H, d), 3.98(3H, s), 2.37(3H, s).

Mass (m/e) = 381 [M^++1]$^+$

Preparation 89

Synthesis of 8-bromo-2-(3-chloro-4-methoxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 88(14.2g, 37.2mmol) was added to methanol(200㎖), and then 2M aqueous sodium hydroxide solution(55.8㎖, 3eq.) and 34% aqueous hydrogen peroxide(12.6㎖, 3eq.) were added thereto. After stirring for 3 hours at

room temperature, the reaction solution was neutralized by 2M aqueous hydrochloric acid solution, diluted with water(200㎖), and filtered. The solid thus obtained was washed with water and methanol to give 9.17g(Yield 65.7%) of the purified title compound.

^{1}H NMR ($CDCl_3$, ppm) : 8.43(1H, s), 8.30(1H, d), 7.96(1H, s), 7.77(1H, s), 7.10(1H, d), 6.96(1H, br s), 3.99(3H, s), 2.46(3H, s).

Mass (m/e) = 395$[M^+ + 1]^+$

Preparation 90

Synthesis of 8-bromo-2-(3-chloro-4-methoxyphenyl)-3-methoxy-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 89(9.17g, 24.4mmol) was heated under reflux together with iodomethane(5.2g, 1.5eq.) and potassium carbonate(4.4g, 1.3molar eq.) in acetone(100㎖) for 5 hours. After completion of reaction, the reaction solution was cooled to room temperature and then filtered. The solid thus obtained was washed with water and acetone to give 8.0g (Yield 79.8%) of the purified title compound.

^{1}H NMR ($CDCl_3$, ppm) : 8.33(1H,s), 8.22(1H,d), 7.97(1H,s), 7.73(1H,s), 7.08(1H,d), 3.99 (3H,s), 3.92(3H,s), 2.45(3H,s).

Mass (m/e) = 409$[M^+ + 1]^+$

Preparation 91

Synthesis of 2-(3-chloro-4-methoxyphenyl)-3-methoxy-6-methyl-8-(4-pyridinyl)-4*H*-chromen-4-one

The compound prepared in Preparation 90(3.0g, 7.32mmol), 1.5 equivalent of bispinacolatodiboron(2.8g), 5mol% of dichlorobistriphenylphosphinepalladium and 3 equivalents of potassium acetate(2.15g) were dissolved in dimethylformamide solvent(20 ㎖), and the resulting mixture was reacted under nitrogen gas for 2 hours at 80℃. After the reaction solution was cooled to room temperature, 2 equivalents of 4-bromopyridine

hydrochloride, 5mol% of dichlorobistriphenylphosphinepalladium and 2M sodium carbonate solution(18.3㎖, 5 eq.) were added thereto and the resulting mixture was stirred under nitrogen gas for 15 hours at 80℃. The reaction solution was filtered and washed with dimethylformamide and 10% methanol/methylene chloride. The filtrate was concentrated and the residue was treated with water(30㎖). The pale yellow solid thus obtained was filtered, washed with water and acetone, and dried to give 2.1g(Yield 70%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm) : 8.78(2H, d), 8.12(1H, s), 8.06(1H, s), 7.91(1H, d), 7.55(3H, m), 6.97 (1H, d), 3.96 (3H, s), 3.94(3H, s), 2.52(3H, s).

Mass (m/e) = 408 $[M^+ + 1]^+$

Preparation 92

Synthesis of 4-[2-(3-chloro-4-methoxyphenyl)-3-methoxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1-methylpyridinium iodide

The compound prepared in Preparation 91(2.1g, 51.5mmol) was refluxed together with 2 equivalents of iodomethane in acetonitrile solvent(30㎖) for 3 hours. The reaction solution was concentrated. To the residue was added methanol, which was then stirred, filtered, and washed with methanol to give 2.44g(Yield 86%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : 9.15(2H, d), 8.57(2H, d), 8.13(1H, s), 7.97(2H, m), 7.88(1H, d), 7.31(1H, d), 4.41(3H, s), 3.95(3H, s), 3.85(3H, s), 2.54(3H, s).

Mass (m/e) = 423$[M^+]$

Preparation 93

Synthesis of 2-(3-chloro-4-methoxyphenyl)-3-methoxy-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one

The compound prepared in Preparation 92(2.44g, 4.43mmol) was reacted under 1atm of hydrogen in 5mol% Pt_2O, 50% methanol/dichloromethane solvent for 48 hours.

The reaction mixture was filtered through a cellite pad and concentrated to give 2.3g(Yield 93%) of the title compound in the form of hydriodate.

^{1}H NMR ($CDCl_3$, ppm) : 8.09(1H, d), 7.95(2H, s), 7.44(1H, s), 7.10(1H, d), 4.00(3H, s), 3.93(3H, s), 3.77(2H, m), 3.57(1H, m), 3.03(2H, m), 2.85(3H, s), 2.74(2H, m), 2.46(3H, s), 2.23(2H, m).

Mass (m/e) = 428$[M^+ +1]^+$

Example 38

Synthesis of 2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 38)

The compound prepared in Preparation 93(2.3g, 4.13mmol) was dissolved in dichloromethane(50㎖), 5 equivalents of borontribromide was added thereto, and the resulting mixture was reacted for 10 hours at room temperature. The remaining borontribromide was decomposed by methanol and concentrated under reduced pressure. The solid thus obtained was washed with 10% methanol/dichloromethane to give 1.93g(Yield 97%) of the title compound in the form of hydrobromide having a yellow color.

^{1}H NMR (DMSO-d_6, ppm) : 9.60(1H, br s), 8.23(1H, s), 8.01(1H, d), 7.77(1H, s), 7.47(1H, s), 7.19(1H, d), 5.75(1H, s), 3.61-3.42(5H, m), 2.87(3H, s), 2.44(3H, s), 2.05(2H, m), 1.90(2H, m).

Mass (m/e) = 400$[M^+ +1]^+$

Example 39

Synthesis of 2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-8-(4-pyridinyl)-4*H*-chromen-4-one(Compound 39)

The compound prepared in Preparation 91(145mg, 0.357mmol) was reacted according to the same procedure as Example 38 to give 156mg(Yield 94.8%) of the title

compound in the form of hydrobromide.

^{1}H NMR (CD_3OD, ppm) : 10.90(1H, br s), 9.80(1H, br s), 8.99(2H, s), 8.20(2H, s), 8.07(1H, s), 8.02(1H, s), 7.84(2H, m), 7.09(1H, d), 2.49(3H, s).

Mass (m/e) = 380[M^++1]$^+$

Example 40

Synthesis of 4-[2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1-methylpyridinium bromide(Compound 40)

The compound prepared in Preparation 92(30mg, 0.054mmol) was reacted according to the same procedure as Example 38 to give 15mg(Yield 58%) of the title compound in the form of hydrobromide.

^{1}H NMR (DMSO-d_6, ppm) : 10.94(1H, s), 9.82(1H, s), 9.17(2H, d), 8.56(2H, d), 8.12(2H, d), 7.92(1H, s), 7.75(1H, d), 7.10(1H, d), 4.42(3H, s), 2.53(3H, s).

Mass (m/e) = 394[M^+]

Preparation 94

Synthesis of 2-(4-methoxyphenyl)-3-methoxy-6-methyl-8-(4-pyridinyl)-4*H*-chromen-4-one

1-(3-Bromo-2-hydroxy-5-methylphenyl)-1-ethanone(500mg, 2.18mmol) and 4-methoxybenzaldehyde(0.36g, 1.2molar eq.) were reacted according to the same procedure as Preparations 88, 89, 90 and 91 to give 417mg(Total Yield 51%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm): 8.74(2H, d), 8.12(1H, s), 7.92(2H, d), 7.57(2H, d), 7.50(1H, s), 6.94(2H, d), 3.88(3H, s), 3.85(3H, s), 2.50(3H, s)

Mass (m/e) = 374[M^++1]$^+$

Preparation 95

Synthesis of 2-(4-methoxyphenyl)-3-methoxy-6-methyl-8-(1-methyl-4-

piperidinyl)-4*H*-chromen-4-one

The compound prepared in Preparation 94(100mg, 0.268mmol) was reacted according to the same procedure as Preparations 92 and 93 to give 108mg(Total Yield 85%) of the title compound in the form of hydriodate.

^{1}H NMR (DMSO-d_6, ppm) : 8.16(2H, d), 7.86(1H, s), 7.49(1H, s), 6.97(2H, d), 3.90(3H, s), 3.89(3H, s), 3.60(3H, m), 2.91(5H, m), 2.52(3H, s), 2.22-2.20(4H, m).

Mass (m/e) = 394 $[M^+ + 1]^+$

Example 41

Synthesis of 2-(4-hydroxyphenyl)-3-hydroxy-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 41)

The compound prepared in Preparation 95(50mg, 0.095mmol) was reacted according to the same procedure as Example 38 to give 35mg(Yield 82%) of the title compound in the form of hydrobromide.

^{1}H NMR (CD_3OD, ppm) : 8.16(2H, d), 7.86(1H, s), 7.49(1H, s), 6.97(2H, d), 3.67(3H, m), 3.35(2H, m), 2.91(3H, s), 2.47(3H, s), 2.26(2H, m), 2.07(2H, m).

Mass (m/e) = 366 $[M^+ + 1]^+$

Preparation 96

Synthesis of 2-(3-methyl-4-methoxyphenyl)-3-methoxy-6-methyl-8-(4-pyridinyl)-4*H*-chromen-4-one

1-(3-Bromo-2-hydroxy-5-methylphenyl)-1-ethanone(500mg, 2.18mmol) and 3-methyl-4-methoxybenzaldehyde(0.4g, 1.2molar eq.) were reacted according to the same procedure as Preparations 88, 89, 90 and 91 to give 252mg(Total Yield 30%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm) : 8.76(2H, d), 8.13(1H, s), 7.90(1H, d), 7.76(1H, s),

7.56(2H, d), 7.52(1H, s), 6.87(1H, d), 3.90(3H, s), 3.89(3H, s), 2.52(3H, s)

Mass (m/e) = 388[M^++1]$^+$

Preparation 97

Synthesis of 2-(3-methyl-4-methoxyphenyl)-3-methoxy-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one

The compound prepared in Preparation 96(252mg, 0.65mmol) was reacted according to the same procedure as Preparations 92 and 93 to give 178mg(Total Yield 51%) of the title compound in the form of hydriodate.

^{1}H NMR ($CDCl_3$+CD_3OD, ppm) : 7.90(1H, s), 7.86(1H, d), 7.77(1H, s), 7.40(1H, s), 6.96(1H, d), 3.89(3H, s), 3.80(3H, s), 3.64(2H, m), 3.50(1H, m), 2.91(2H, m), 2.76(3H, s), 2.42(3H, s), 2.26(3H, s), 2.22-2.20(4H, m).

Mass (m/e) = 408 [M^++1]$^+$

Example 42

Synthesis of 3-hydroxy-2-(4-hydroxy-3-methylphenyl)-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 42)

The compound prepared in Preparation 97(178g, 0.332mmol) was reacted according to the same procedure as Example 38 to give 115mg(Yield 75%) of the title compound in the form of hydrobromide.

^{1}H NMR (CD_3OD, ppm) : 8.02(1H, s), 7.96(1H, d), 7.85(1H, s), 7.50(1H, s), 6.92(1H, d), 3.69(3H, m), 3.44(2H, m), 2.98(3H, s), 2.48(3H, s), 2.30(5H, m), 2.10(2H, m).

Mass (m/e) = 380[M^++1]$^+$

Preparation 98

Synthesis of 2-(3-trifluoromethyl-4-methoxyphenyl)-3-methoxy-6-methyl-8-(4-pyridinyl)-4*H*-chromen-4-one

1-(3-Bromo-2-hydroxy-5-methylphenyl)-1-ethanone(500mg, 2.18mmol) and 3-trifluoromethyl-4-methoxybenzaldehyde(0.4g, 1.2molar eq.) were reacted according to the same procedure as Preparations 88, 89, 90, and 91 to give 252mg(Total Yield 30%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm) : 8.75(2H, d), 8.20(2H, m), 8.10(1H, s), 7.50(4H, m), 7.05(1H, d), 3.95 (3H, s), 3.92(3H, s), 2.51(3H, s).

Mass (m/e) = 442$[M^+$+1$]^+$

Preparation 99

Synthesis of 2-(3-trifluoromethyl-4-methoxyphenyl)-3-methoxy-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one

The compound prepared in Preparation 98(100mg, 0.226mmol) was reacted according to the same procedure as Preparations 92 and 93 to give 100mg(Total Yield 75%) of the title compound in the form of hydriodate.

^{1}H NMR (DMSO-d_6, ppm) : 8.64(1H, s), 8.25(1H, s), 7.81(1H, s), 7.45(1H, s), 7.22(1H, d), 4.00(3H, s), 3.96(3H, s), 3.65-3.30(5H, m), 2.89(3H, s), 2.46(3H, s), 2.21(2H, m), 1.94(2H, m).

Mass (m/e) = 462$[M^+$+1$]^+$

Example 43

Synthesis of 3-hydroxy-2-(4-hydroxy-3-trifluoromethylphenyl)-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 43)

The compound prepared in Preparation 99(100mg, 0.169mmol) was reacted according to the same procedure as Example 38 to give 69mg(Yield 79%) of the title compound in the form of hydrobromide.

^{1}H NMR (DMSO-d_6, ppm) : 9.60(1H, br s), 9.39(1H, s), 8.66(1H, s), 8.30(1H, d),

7.79(1H, s), 7.46(1H, s), 6.84(1H, d), 4.39(1H, m), 3.65-3.33(4H, m), 2.92(3H, s), 2.43(3H, s), 2.32(2H, m), 2.14(2H, m).

Mass (m/e) = 434$[M^{+}+1]^{+}$

Preparation 100

Synthesis of 4-[2-(3-chloro-4-methoxyphenyl)-3-methoxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1-(2-methoxyethyl)pyridinium bromide

The compound prepared in Preparation 91(50mg, 0.122mmol) was refluxed with 2 equivalents of 2-bromoethyl methyl ether in acetonitrile solvent(5㎖) for 3 hours. The reaction solution was concentrated and the residue was treated with methanol, filtered, and washed with methanol to give 52mg(Yield 78%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : 9.15(2H, d), 8.57(2H, d), 8.13(1H, s), 7.97(2H, m), 7.88(1H, d), 7.31(1H, d), 4.41(3H, s), 3.95(6H, d), 3.85(3H, s), 3.80(2H, t), 2.54(3H, s).

Mass (m/e) = 466$[M^{+}]$ms=545

Preparation 101

Synthesis of 2-(3-chloro-4-methoxyphenyl)-3-methoxy-8-[1-(2-methoxyethyl)-4-piperidinyl]-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 100(45mg, 0.082mmol) was reacted according to the same procedure as Preparation 93 to give 30mg(Yield 66%) of the title compound in the form of hydrobromide.

^{1}H NMR ($CDCl_3$, ppm) : 8.09(1H, d), 7.95(2H, s), 7.44(1H, s), 7.10(1H, d), 4.00(3H, s), 3.93(6H, d), 3.80(2H, t), 3.77(4H, m), 3.57(1H, m), 3.03(2H, m), 2.85(3H, s), 2.74(2H, m), 2.46(3H, s), 2.23(2H, m).

Mass (m/e) = 472$[M^{+}+1]^{+}$

Example 44

Synthesis of 2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-8-[1-(2-hydroxy-ethyl)-4-piperidinyl]-6-methyl-4*H*-chromen-4-one

The compound prepared in Preparation 101(25mg, 0.045mmol) was reacted according to the same procedure as Example 38 to give 15mg(Yield 65%) of the title compound in the form of hydrobromide.

^{1}H NMR (DMSO-d_6, ppm) : 9.60(1H, br s), 8.23(1H, s), 8.01(1H, d), 7.77(1H, s), 7.47(1H, s), 7.19(1H, d), 5.75(1H, s), 3.61-3.42(7H, m), 2.87(2H, m), 2.44(3H, s), 2.05(2H, m), 1.90(2H, m).

Mass (m/e) = 430[M^++1]$^+$

Preparation 102

Synthesis of 4-[2-(3-chloro-4-methoxyphenyl)-3-methoxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]pyridinium bromide

The compound prepared in Preparation 91(50mg, 0.122mmol) was reacted with 2 equivalents of N-(2-bromoethyl)phthalimide according to the same procedure as Preparation 100 to give 60mg(Yield 74%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : 9.15(2H, d), 8.57(2H, d), 8.13(1H, s), 7.97(2H, m), 7.88(1H, d), 7.55-7.40(4H, m), 7.31(1H, d), 4.41(2H, m), 3.95(3H, s), 3.85(3H, s), 2.54(3H, s), 2.23(2H, t).

Mass (m/e) = 581[M+]ms=660

Preparation 103

Synthesis of 2-(2-{4-[2-(3-chloro-4-methoxyphenyl)-3-methoxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1-piperidinyl}ethyl)-2*H*-isoindol-1,3(2*H*)-dione

The compound prepared in Preparation 102(50mg, 0.075mmol) was reacted

according to the same procedure as Preparation 93 to give 45mg(Yield 89%) of the title compound in the form of hydrobromide.

^{1}H NMR (DMSO-d_6, ppm) : 8.09(1H, d), 7.95(2H, s), 7.58-7.47(4H, m), 7.44(1H, s), 7.10(1H, d), 4.00(3H, s), 3.93(3H, s), 3.77(2H, m), 3.57(1H, m), 3.03(2H, m), 2.85(2H, s), 2.74(2H, m), 2.46(3H, s), 2.23(4H, m).

Mass (m/e) = 587[M^++1]$^+$

Preparation 104

Synthesis of 2-(2-{4-[2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1-piperidinyl}ethyl)-2*H*-isoindol-1,3(2*H*)-dione

The compound prepared in Preparation 103(40mg, 0.060mmol) was reacted according to the same procedure as Example 38 to give 25mg(Yield 65%) of the title compound in the form of hydrobromide.

^{1}H NMR (DMSO-d_6, ppm) : 9.60(1H, br s), 8.23(1H, s), 8.01(1H, d), 7.77(1H, s), 7.62-7.49(4H, m), 7.47(1H, s), 7.19(1H, d), 5.75(1H, s), 3.61-3.42(5H, m), 2.87(2H, t), 2.44(3H, s), 2.23(2H, t), 2.05(2H, m), 1.90(2H, m).

Mass (m/e) = 559[M^++1]$^+$

Example 45

Synthesis of 8-[1-(2-aminoethyl)-4-piperidinyl]-2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 45)

The compound prepared in Preparation 104(25mg, 0.040mmol) was introduced into ethanol(5㎖), 3 equivalents of hydrazine was added thereto, and the resulting mixture was heated to 60℃ for 1 hour. After the reaction solution was cooled to room temperature, aqueous sodium carbonate solution was added. The resulting solid was filtered to give 12mg(Yield 70%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : 9.60(1H, br s), 8.23(1H, s), 8.01(1H, d), 7.77(1H, s),

7.47(1H, s), 7.19(1H, d), 5.75(1H, s), 3.61-3.42(5H, m), 2.87(2H, t),2.55(2H, t), 2.44(3H, s), 2.05(2H, m), 1.90(2H, m).

Mass (m/e) = 429[M^++1]$^+$

Experiment 1

Inhibitory activity against CDK2 and CDK4

The inhibitory activity against CDK2 was measured by referring to Kitagawa, M. et al., *Oncogene 9*; 2549, 1994 and that against CDK4 was measured by referring to Carlson, B.A. et al., *Cancer Research 56*; 2473, 1996.

Active CDK2/cyclin A used in this experiment is a conjugate of human CDK2 protein labelled with histidine and cyclin A protein; is purified from an insect cell infected both with baculovirus expressing His-CDK2 gene and baculovirus expressing cyclin A gene; and has a unit activity of 14nmole/min/㎎ and Km value against ATP of 22μ M. Active CDK4/cyclin D1 used in this experiment is a conjugate of human CDK4 protein bound to GST(glutathione-S-transferase) and cyclin D1 protein; is expressed and purified from an insect cell; and has a unit activity of 57nmole/min/㎎ and Km value against ATP of 940μ M. The part of amino acid positions 780 to 928 of C-terminus of human Rb protein was isolated, N-terminus thereof was labelled with GST protein, large amount thereof was expressed in bacteria and purified to be used as the substrate for the enzyme.

The activities of CDK2/cyclin A and CDK4/cyclin D1 were determined as follows. About 100ng of enzyme was reacted in a total 100㎕ of 20mM Tris(pH 8.0), 100mM NaCl, 10mM $MgCl_2$ buffer solution containing 20㎍ of GST-Rb protein, 100μ M of ATP and 5μ Ci of p^{32}-γ-ATP at 30℃ for 30 minutes. Then, EDTA was added to a concentration of 20mM to stop the enzyme reaction. Subsequently, 30㎕ of 50% glutathione bead(purchased from Pharmacia) was added to attach GST-Rb to the bead, which was washed three times with 20mM Tris(pH 8.0), 100mM NaCl, 10mM EDTA

solution, and then scintillation counting was carried out. To analyze the inhibitory activity of the compound, the inhibitor having a proper concentration was added to the enzyme reaction solution, and then the enzyme activity was measured according to the above method.

The inhibitory activity against CDK2 and CDK4 of the compound of formula (1) according to the present invention was represented as IC_{50} value(see the following Table 1).

Table 1

Compound No.	FAB MS (M+1)	CDK2 IC_{50} (μ M)	CDK4 IC_{50} (μ M)
1	299	1.4	20.0
2	359	4.5	7.7
3	371	6.0	3.9
4	284	2.1	2.1
6	326	30.0	10.0
7A	383	18.0	47.0
7B	341	3.0	17.0
9	302	14.0	16.0
10	385	30.0	100.0
11	283	150.0	50.0
12	284	2.0	2.1
13	301	1000.0	50.0
14	363	500.0	11.0
15	388	0.250	0.550
16	406	0.450	1.100
17	422	0.185	0.195
18	466	0.075	0.210
19	413	1.400	0.790
20	404	1000	500
21	424	13.00	24.00
22	402	0.700	2.000
23	418	1.500	5.000

24	456	0.250	2.100
25	389	0.088	1.2
26	417	0.22	0.71
27	445	9	7.1
28	479	2.24	3.2
29	472	1.8	1.7
30	471	5.6	1.6
31	465	1.4	3
32	403	0.224	0.54
33	447	0.6	0.9
34	465	1.3	1.8
35	423	0.07	0.18
36	451	0.5	0.6
37	437	0.2	0.18
38	400	0.50	0.12
39	380	0.13	0.28
40	394	0.70	0.31
41	366	0.56	0.15
42	380	0.178	0.65
43	434	6.3	<1
44	430	<1	<1
45	429	<1	<1

Experiment 2

Acute toxicity test

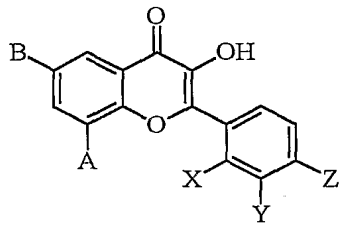
To determine the acute oral toxicities of the test compounds, solutions containing a compound in different concentrations from each other were administered orally to ICR male mouse with a dose of 10㎖/kg body weight. After oral administration, lethality and symptoms for 7 days were observed, and LD_{50}(㎎/kg) was calculated according to Litchfield-Wilcoxon method. The results are represented in the following Table 2.

Table 2

Test Compound	LD_{50} (mg/kg)
Example 15	>3,000
Example 17	>3,000
Example 36	>3,000
Example 37	>3,000
Example 38	>3,000
Example 40	>3,000

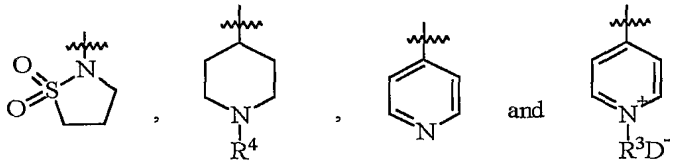
CLAIMS

1. A compound represented by the following formula (1):



(1)

in which

A represents hydrogen or nitro, or represents amino which is optionally substituted by C_1-C_4-alkylcarbonyl or carbamoyl, or represents a structure selected from a group consisting of  wherein R^4 represents hydrogen or C_1-C_6-alkyl which is optionally substituted by amino or hydroxy, R^3 represents C_1-C_6-alkyl which is optionally substituted by amino or hydroxy and D represents halogen,

B represents methyl, or represents amino which is optionally mono- or disubstituted by substituents selected from a group consisting of C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, acetyl, phenyl, benzyl and piperidinyl,

X, Y and Z independently of one another represent hydrogen, hydroxy, nitro, cyano or halogen, or represent amino which is optionally substituted by C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl or carbamoyl, or represent C_1-C_4-alkyl which is optionally substituted by hydroxy or halogen, pharmaceutically acceptable salt, hydrate, solvate or isomer thereof.

2. The compound of claim 1 selected from a group consisting of the following:

8-amino-2-(3-amino-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one (Compound 1);

2-(4-hydroxy-3-nitrophenyl)-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one (Compound 2);

N-[2-(4-hydroxy-3-nitrophenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl] acetamide(Compound 3);

8-amino-2-(4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 4);

2-(3-amino-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 5);

N-[2-hydroxy-5-(3-hydroxy-6-methyl-4-oxo-4*H*-chromen-2-yl)phenyl]acetamide (Compound 6);

N-{2-[4-hydroxy-3-(isopropylamino)phenyl]-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl}acetamide(Compound 7A);

N-[2-(3-amino-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]acetamide(Compound 7B);

2-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-6-methyl-8-nitro-4*H*-chromen-4-one (Compound 8);

8-amino-2-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one (Compound 9);

N-{5-[8-(ureido)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-2-yl]-2-hydroxyphenyl} urea(Compound 10);

8-amino-2-(4-aminophenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 11);

8-amino-3-hydroxy-2-(3-hydroxyphenyl)-6-methyl-4*H*-chromen-4-one(Compound 12);

3-hydroxy-6-methyl-2-(2,3,4-trihydroxyphenyl)-4*H*-chromen-4-one(Compound 13);

2-(2-bromo-3,4-dihydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one (Compound 14);

2-[3-hydroxy-2-(4-hydroxyphenyl)-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 15);

2-[2-(3-fluoro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 16);

2-[2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 17);

2-[2-(3-bromo-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 18);

5-[8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-2-yl]-2-hydroxybenzonitrile(Compound 19);

2-[2-(2,4-dihydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 20);

2-[2-(3-chloro-4-fluorophenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 21);

2-[3-hydroxy-2-(4-hydroxy-3-methylphenyl)-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 22);

2-{3-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]-6-methyl-4-oxo-4*H*-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione(Compound 23);

2-[3-hydroxy-2-(4-hydroxy-3-trifluoromethylphenyl)-6-methyl-4-oxo-4*H*-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 24);

2-[6-amino-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 25);

2-[6-(dimethylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 26);

2-[6-(diethylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 27);

2-[6-(benzylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ

^{6}-isothiazolidin-1,1-dione(Compound 28);

2-[3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-6-(4-piperidinylamino)-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 29);

2-[6-(cyclohexylamino)-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 30);

2-[6-anilino-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 31);

2-[3-hydroxy-2-(4-hydroxyphenyl)-6-(methylamino)-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 32);

2-{3-hydroxy-6-[(2-hydroxyethyl)(methyl)amino]-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl}-1λ ^{6}-isothiazolidin-1,1-dione(Compound 33);

N-[2-(3-chloro-4-hydroxyphenyl)-8-(1,1-dioxo-1λ ^{6}-isothiazolidin-2-yl)-3-hydroxy-4-oxo-4H-chromen-6-yl]acetamide(Compound 34);

2-[6-amino-2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 35);

2-[2-(3-chloro-4-hydroxyphenyl)-6-(dimethylamino)-3-hydroxy-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 36);

2-[2-(3-chloro-4-hydroxyphenyl)-6-(methylamino)-3-hydroxy-4-oxo-4H-chromen-8-yl]-1λ ^{6}-isothiazolidin-1,1-dione(Compound 37);

2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 38);

2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-8-(4-pyridinyl)-4*H*-chromen-4-one(Compound 39);

4-[2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4-oxo-4*H*-chromen-8-yl]-1-methylpyridinium bromide(Compound 40);

2-(4-hydroxyphenyl)-3-hydroxy-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 41);

3-hydroxy-2-(4-hydroxy-3-methylphenyl)-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 42);

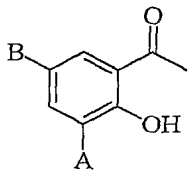
3-hydroxy-2-(4-hydroxy-3-trifluoromethylphenyl)-6-methyl-8-(1-methyl-4-piperidinyl)-4*H*-chromen-4-one(Compound 43);

2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-8-[1-(2-hydroxyethyl)-4-piperidinyl]-6-methyl-4*H*-chromen-4-one(Compound 44); and

8-[1-(2-aminoethyl)-4-piperidinyl]-2-(3-chloro-4-hydroxyphenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one(Compound 45).

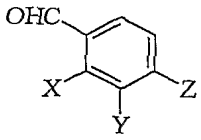
3. A process for preparing the compound of formula (1) as defined in claim 1 characterized in that

(a) a compound represented by the following formula (5):



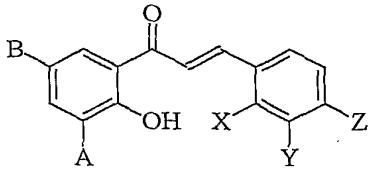
(5)

in which A and B are defined as claim 1, is reacted with an aldehyde represented by the following formula (6):



(6)

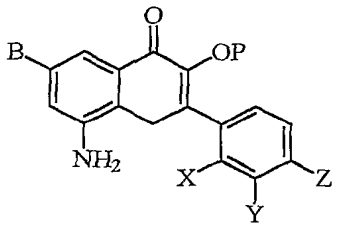
in which X, Y and Z are defined as claim 1, to produce a compound represented by the following formula (7):



(7)

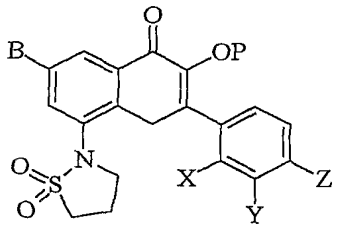
in which A, B, X, Y and Z are defined as claim 1, and the compound of formula (7) thus prepared is cyclized in the presence of a base to produce the compound of formula (1) as defined in claim 1;

(b) a compound represented by the following formula (8):



(8)

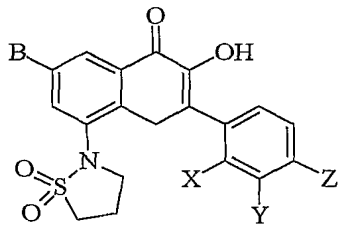
in which B, X, Y and Z are defined as claim 1 and P represents hydroxy-protecting group, is reacted with 3-chloropropanesulfonylchloride in the presence of a base and a catalyst to produce a compound represented by the following formula (9):



(9)

in which B, X, Y and Z are defined as claim 1 and P is defined as previously described, and the compound of formula (9) thus prepared is deprotected to produce a compound

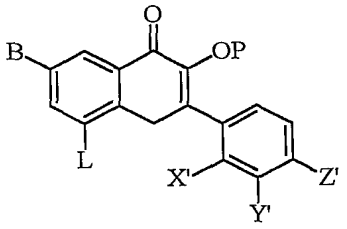
represented by the following formula (1a):



(1a)

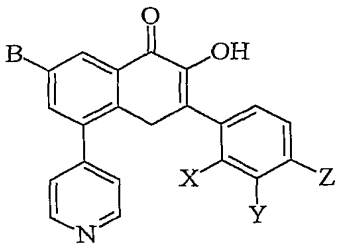
in which B, X, Y and Z are defined as claim 1;

(c) a compound represented by the following formula (10):



(10)

in which B is defined as claim 1 and P is defined as previously described, L represents leaving group, and X', Y' and Z' each are identical with X, Y and Z, respectively, but hydroxy group(s) is(are) protected, is reacted with 4-halogenopyridine in the presence of a base and a catalyst and then deprotected to produce a compound represented by the following formula (1b):



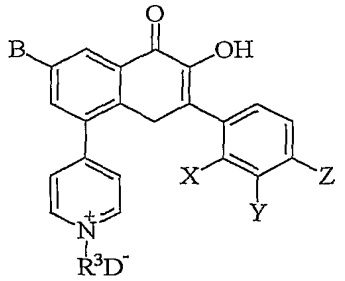
(1b)

in which B, X, Y and Z are defined as claim 1;

(d) the compound obtained before the deprotection step in process variant (c) is reacted with a compound represented by the following formula (11):

R^3D (11) .

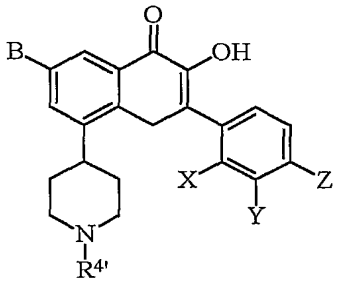
in which R^3 and D are defined as claim 1, and then deprotected to produce a compound represented by the following formula (1c):



(1c) .

in which B, X, Y, Z, R^3 and D are defined as claim 1;

(e) the compound obtained before the deprotection step in process variant (d) is reduced and deprotected to produce a compound represented by the following formula (1d):



(1d) .

in which B, X, Y and Z are defined as claim 1 and $R^{4'}$ is identical with R^4 but other than hydrogen;

or further hydrolysis, protection, deprotection, reduction or amidation reaction may be carried out.

4. A composition for suppression or treatment of cancer and diseases induced by cell proliferation such as inflammation, angiostenosis, angiogenesis, etc. which comprises the compound of formula (1), pharmaceutically acceptable salt, hydrate, solvate, or isomer thereof, as defined in claim 1, as an active component together with pharmaceutically acceptable carries.

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/KR01/00725

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 311/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

IPC7 C07D, A61K

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

KR: IPC as above

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)

CAPLUS(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2000/12496 A1(LG Chemical Ltd.,) 09 MARCH 2000 See example, claim	1, 4
A	WO 97/29779 A2(Regents of the University of Minnesota) 21 AUGUST 1997 See the whole document	1
A	WO98/17662 A1(CIBA GEIGY AG, TRAXLER PETER, SEQUIN URS, GREEN JENNIFER MARY, FURET PASCAL) 30 APRIL 1998 See the whole document	1
A	JP63-2925 A2(Nippon Kayaku Co., Ltd.) 07 January 1988 See the whole document	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* *Special categories of cited documents:*

"A" document defining the general state of the art which is not considered to be of particular relevence

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" *later document published after the international filing date or priority* date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 AUGUST 2001 (31.08.2001)	31 AUGUST 2001 (31.08.2001)

Name and mailing address of the ISA/KR	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR01/00725

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		AU 5531599 A1	21. 03. 2000
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		AU 4947997 A1	15. 05. 98